S. HRG. 109–816

NOMINATION

OF

ANDREW VON ESCHENBACH AND PAUL DECAMP

HEARING

OF THE

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

ONE HUNDRED NINTH CONGRESS

SECOND SESSION

ON

ANDREW VON ESCHENBACH, OF TEXAS, TO BE COMMISSIONER OF FOOD AND DRUGS, DEPARTMENT OF HEALTH AND HUMAN SERVICES

PAUL DeCAMP, OF VIRGINIA, TO BE ADMINISTRATOR OF THE WAGE AND HOUR DIVISION, DEPARTMENT OF LABOR

AUGUST 1, 2006

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NOMINATION OF ANDREW VON ESCHENBACH and PAUL DeCAMP

TUESDAY, AUGUST 1, 2006

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

The committee met, pursuant to notice, at 10 a.m., in room SD–430, Dirksen Senate Office Building, Hon. Mike Enzi, chairman of the committee, presiding.

Present: Senators Enzi, Alexander, Isakson, Ensign, Hatch, Kennedy, Dodd, Harkin, Mikulski, Murray, Reed and Clinton.

Also present: Senator Hutchison.

OPENING STATEMENT OF SENATOR ENZI

The CHAIRMAN. Good morning, and welcome to the confirmation hearing for Dr. Andrew von Eschenbach, to be the Commissioner of the Food and Drug Administration and Mr. Paul DeCamp, to be the Wage and Hour Administrator of the Department of Labor. Both nominees are superbly qualified for these positions, and I look forward to their testimony and responses today.

The FDA has a very broad and critical mission in protecting the public health. Dr. von Eschenbach, you'll be in charge of an Agency that regulates $1 trillion worth of products a year. The FDA ensures safety and effectiveness for all drugs and 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'll 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. As a physician, I know you take this mission to heart.

I'm pleased that we are now ready to hear Dr. von Eschenbach's plan to take charge, to take action, and to take responsibility for leading the FDA in the best interests of public health. We've met several times during your tenure as Acting Commissioner, and discussed a variety of issues, including drug safety, advisory committees, and citizen petitions. At those meetings, I've been impressed by your dedication to solving problems, and your focus on patient care, and your knowledge. One item we've discussed many times is the application to make the Plan B emergency contraceptive available without a prescription. You made a major announcement

about that yesterday, and I'm going to ask you to go over that in some detail later this morning.

The FDA has been without a confirmed Commissioner for all but 18 months out of the last 5½ years. I think we all can agree we need a strong leader at the FDA right now, and one who has a mandate to act. We must be forward-looking. There are many items before the FDA that require the immediate attention of an FDA Commissioner vested with full authority. But that authority flows directly from the act of Senate confirmation. Without a Senate-confirmed leader, we can't expect the FDA to be as effective as we need it to be. I urge my colleagues to consider this as we move forward.

I look forward to working with you, Senator Kennedy, and with members of the committee, to protect and promote the public health and to maintain the FDA's status as one of the world's strongest regulatory agencies. We've been working in a very bipartisan way to get a bill that we think will do that. A confirmed commissioner would be very helpful in that.

Also on this morning's agenda is the nomination of Paul DeCamp to be the Wage and Hour Administrator. This position within the Department of Labor is a pivotal one in administering and enforcing some of our most important workplace laws. The Wage and Hour Division is an integral part of the Department's largest administrative component, the Employment Standards Administration. The Wage and Hour Division is responsible for administering the minimum wage, overtime pay, and child labor provisions of the Fair Labor Standards Act. This statute has enormous reach, covering some 110 million full-time and part-time workers.

In addition to the Fair Labor Standards Act, the Wage and Hour Division is responsible for the administration and enforcement of a number of other important workplace laws, including the Family and Medical Leave Act, the Migrant and Seasonal Workers Protection Act, and the three major statutes governing wage and hour standards for government contracts: the Davis-Bacon Act, the McNamara-O'Hara Service Contract Act, and the Walsh-Healy Public Contracts Act.

The Wage and Hour Administrator oversees many of the laws that protect our Nation's greatest resource: our workers. The President's nominee for this important position, Paul DeCamp, is currently serving in the Department of Labor as senior policy advisor to the Assistant Secretary of Labor for Employment Standards.

Before assuming his current position at the Department of Labor, Mr. DeCamp had a distinguished career in a private legal practice, where he specialized in labor and employment issues, with a special emphasis on wage and hour matters. He has also written extensively on a number of Fair Labor Standards Act issues. The combination of practical front-line experience and demonstrated intellectual interest in the workings of the Wage and Hour Administration will be invaluable as he assumes his position of leading the division.

Following an outstanding career at Harvard College and Columbia Law School, Mr. DeCamp was selected for a clerkship with U.S. Circuit Judge Alan E. Norris of the Sixth Circuit Court of Appeals. Judge Norris has recommended Mr. DeCamp to this committee

without reservation, praising his intellectual abilities, his practicality, balance, and impartiality in resolving difficult legal issues. He and others who have written to the committee in support of Mr. DeCamp's nomination praise his judgment, unbiased analysis of legal issues, attention to detail, and his ability to lead others.

Mr. DeCamp, it'll be your responsibility to build upon your record and experience to effectively administer laws that are so critical to American workers and businesses. I have confidence in your ability to do so.

I would note that the committee has received a number of letters in support of both these worthy nominees. These letters of support will be included in the record.

[The information previously referred to follows:]

MEDICAL DEVICE MANUFACTURERS ASSOCIATION (MDMA),
WASHINGTON, DC,
JULY 27, 2006.

Hon. MICHAEL B. ENZI,
Chairman,
Committee on Health, Education, Labor, and Pensions,
835 Hart Senate Office Building,
Washington, DC 20510.

Hon. EDWARD M. KENNEDY,
Ranking Member,
Committee on Health, Education, Labor, and Pensions,
644 Dirksen Senate Office Building,
Washington, DC 20510.

DEAR CHAIRMAN ENZI AND SENATOR KENNEDY: On behalf of the Medical Device Manufacturers Association ("MDMA") and the entrepreneurial and innovative medical technology companies we represent, I wish to convey strong support for the speedy confirmation of Dr. Andrew von Eschenbach to be the Commissioner of the Food and Drug Administration. A rapid confirmation process is critical to ensuring the public health and safety of the Nation's citizens.

As a representative of the innovative sector of the medical technology industry, MDMA has worked with Dr. von Eschenbach 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. von Eschenbach, as both a physician and a cancer survivor, is uniquely suited to lead FDA. With rapidly developing technologies and advancements in medicine it is imperative that FDA have a Commissioner who possesses not only the appropriate professional training, but also the courage, dedication and integrity necessary to lead the Agency. Dr. von Eschenbach is clearly qualified to be just such a Commissioner. We endorse Dr. von Eschenbach and encourage the Senate to act quickly to confirm him.

Sincerely,

MARK B. LEAHEY,
Executive Director,
Medical Device Manufacturers Association.

NATIONAL ALLIANCE ON MENTAL ILLNESS (NAMI),
ARLINGTON, VA 22201–3042,
July 31, 2006.

Hon. MIKE ENZI,
Hon. EDWARD M. KENNEDY,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, DC 20510.

DEAR CHAIRMAN ENZI & SENATOR KENNEDY: On behalf of the 210,000 members and 1,200 affiliates of the National Alliance on Mental Illness (NAMI), I am writing to urge support for the nomination of Andrew C. von Eschenbach, M.D. as Commissioner of the Food and Drug Administration (FDA). As the Nation's largest organization representing individuals with severe mental illnesses and their families, NAMI is pleased to support this important appointment.

In NAMI's view, Dr. von Eschenbach brings unique qualifications to the important position of FDA Commissioner. He has an enormous background as a clinician and researcher and is well qualified to lead the FDA. His resume speaks volumes to his professional accomplishments as a leader in medical research. He most recently served as the Director of the National Cancer Institute as Chief Academic Officer at the M.D. Anderson Cancer Center in Houston. He has gained perspective as a patient advocate, serving as President of the American Cancer Society, before joining NCI and being recognized with the National Health Care Humanitarian Award by the Patient Advocate Foundation in 2005.

NAMI urges you and your colleagues on the Senate HELP Committee to act swiftly on this important nomination. It is critically important that the FDA have a strong leader in place to address challenges faced by the Agency with respect to speeding access to newer and more effective treatments for Americans living with chronic disabling illnesses.

Sincerely,

MICHAEL J. FITZPATRICK, M.S.W.,
Executive Director.

ADVANCED MEDICAL TECHNOLOGY ASSOCIATION (ADVAMED),
WASHINGTON, DC 20005–3814,
July 31, 2006.

Hon. MICHAEL B. ENZI,
Chairman,
Committee on Health, Education, Labor, and Pensions,
428 Dirksen Senate Office Building,
Washington, DC 20510.

Hon. EDWARD M. KENNEDY,
Ranking Member,
Committee on Health, Education, Labor, and Pensions,
317 Russell Senate Office Building,
Washington, DC 20510.

DEAR CHAIRMAN ENZI: On behalf of the Advanced Medical Technology Industry (AdvaMed) and our member companies, I am writing in support of the nomination of Dr. Andrew von Eschenbach to be Commissioner of the Food and Drug Administration.

Dr. von Eschenbach is an excellent choice to head the FDA. He has had an outstanding career as a physician, researcher, and administrator in both the public and private sectors. As a physician, he has treated cancer patients for almost 30 years. As a researcher, he has published more than 200 articles and books and was the founding director of M.D. Anderson's Prostate Cancer Research Program. As an administrator, he has served as Vice President for Academic Affairs at M.D. Anderson and has had a dynamic tenure as the head of the National Cancer Institute. He has also served as the president-elect of the American Cancer Society.

It is critically important to our industry and to the Nation that the position of FDA Commissioner be filled. Strong leadership is essential if the FDA is to most effectively fulfill its mission of assuring that the food Americans eat is safe and healthful, that the drugs they take are safe and effective, and that the medical devices they rely on for cures and treatment are safe and effective and represent the latest and best that our industry can offer. Experience has shown that a permanent director confirmed by the Senate is necessary to assure that the Agency has the authoritative leadership it needs to respond promptly and effectively to all the challenges it faces.

Prompt confirmation of Dr. von Eschenbach is especially important in view of the issues that are currently facing the FDA. Next year, both the medical device and drug user fee programs must be renewed by Congress, and the agreements between industry and the FDA that will be the starting point for the reauthorization are being negotiated right now. The critical path initiative, which offers so much potential for speeding the development and approval of safe and effective products, is just getting off the ground and needs a strong advocate. The challenge of determining how FDA can most effectively conduct post-market surveillance to assure the safety and effectiveness of approved products is an issue that needs strong leadership from the top. The continuing challenges of food safety and preparation for a pandemic or bioterrorist attack need a strong FDA voice.

AdvaMed member companies produce the medical devices, diagnostic products and health information systems that are transforming health care through earlier

disease detection, less invasive procedures and more effective treatments. Our members produce nearly 90 percent of the health care technology purchased annually in the United States and more than 50 percent purchased annually around the world. AdvaMed members range from the largest to the smallest medical technology innovators and companies.

We respectfully urge you to support Dr. von Eschenbach's prompt confirmation. Thank you for considering this request.

Sincerely,

STEPHEN J. UBL,
President and CEO.

OMERIS,
COLUMBUS, OH 43212–1155,
August 2, 2006.

Hon. MICHAEL B. ENZI,
Chairman,
Committee on Health, Education, Labor, and Pensions,
428 Dirksen Senate Office Building,
Washington, DC 20510.

Hon. EDWARD M. KENNEDY, *Ranking Member*
Committee on Health, Education, Labor, and Pensions,
317 Russell Senate Office Building,
Washington, DC 20510.

DEAR CHAIRMAN ENZI: On behalf of Omeris, Ohio's bioscience membership and development organization, and our member companies, I am writing in support of the nomination of Dr. Andrew von Eschenbach to be Commissioner of the Food and Drug Administration.

Dr. von Eschenbach is an excellent choice to head the FDA. He has an outstanding career as a physician, researcher, and administrator in both the public and the private sectors. As a physician, he has treated cancer patients for almost 30 years. As a researcher, he has published more than 200 articles and books and was the founding director of M.D. Anderson's Prostate Cancer Research Program. As an administrator, he has served as the president-elect to the American Cancer Society.

It is critically important to our industry and to the Nation that the position of the FDA Commissioner be filled. Strong leadership is essential if the FDA is to most effectively fulfill its mission of assuring the food Americans eat is safe and healthful, that the drugs they take are safe and effective, and that the medical devices they rely on for cures and treatment are safe and effective and represent the latest and best that our industry can offer. Experience has shown that a permanent director confirmed by the Senate is necessary to assure that the Agency has the authoritative leadership it needs to respond promptly and effectively to all the challenges it faces.

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Omens members, Ohio's bioscience companies, help revitalize our State's economy while developing critical tools, treatments, and technologies that benefit the world. Omens is a focal point for the bioscience and biotechnology community, providing networking and educational events, continually developing web-based resources, addressing public policy, and analyzing resource and funding issues.

We respectfully urge you to support Dr. von Eschenbach's prompt confirmation. Thank you for considering this request.

Sincerely,

ANTHONY J. DENNIS, PH.D.,
President & CEO.

NEW YORK STATE CANCER PROGRAMS ASSOCIATION, INC.,
BUFFALO, NY 14263,
August 3, 2006.

To: SENATE HEALTH, EDUCATION, LABOR, AND PENSIONS COMMITTEE
From: DR. EDWIN A. MIRAND, SECRETARY-TREASURER, NYSCPA

Subject: Nomination of Dr. Andrew von Eschenbach as Permanent Commissioner of Food and Drug Administration

The New York State Cancer Program Association, Inc. supports the nomination by President Bush as permanent Commissioner of Food and Drug Administration (FDA) Dr. Andrew von Eschenbach.

Dr. von Eschenbach's experience as a researcher and physician will provide the FDA with a better focus to confront the challenges and new opportunities facing the Agency. Dr. von Eschenbach will lead the Agency and strengthen the credibility of its decisionmaking process.

EDWIN A. MIRAND, PH.D., D.SC.,
Secretary.

CANCER CURE COALITION,
PALM BEACH GARDENS, FL, 33410,
August 9, 2006.

DR. ANDREW VON ESCHENBACH, M.D.,
Acting Commissioner,
U.S. Food and Drug Administration,
Rockville, MD 20857–0001.

DEAR DR. VON ESCHENBACH: I am President of the Cancer Cure Coalition, a nonprofit Foundation dedicated to the cure and prevention of cancer. We join with the Biotechnology Industry Organization's (BIO) call for a swift confirmation of your appointment as Commissioner of the FDA. We believe it important that a permanent director be in charge of this vitally important public health Agency and we believe that you have the special experience and ability required to deal with the complex problems confronting it.

We believe that the long period where this Agency has lacked a permanent director has led to a slow down in its decisionmaking and a possible fearfulness to approve new scientific breakthroughs. We think that this is holding back important new treatments for life threatening illnesses and in particular those for cancer.

One major example of this is the delay in approving Advexin, a P53 gene tumor suppressor now in Phase III of clinical trials for treating head and neck cancer. This therapy was first developed at the M.D. Anderson Cancer Center in Texas and then was licensed to Introgen Corp. which continued its development. Although being tested for only head and neck cancer this gene therapy has already shown its ability to successfully treat many other types of cancer as well.

The P53 gene is naturally present in the body and it stops cell division when DNA damage occurs. When the P53 gene is damaged or does not function normally genetic mutations can occur in dividing cells leading to the accumulation of malignant cells and potential cancer growth.

What makes this gene therapy even more promising is the recent development by Genzyme Corp. of a new diagnostic test that detects specific mutations in the P53 gene.

This allows the gene therapy treatment to be targeted to those patients most likely to respond to this therapy. Genzyme's test is a significant improvement over the florescent in-situ hybridization. (FISH) technology currently in use.

What is especially troubling about the FDA's delay in approving this therapy is that a similar gene therapy was approved in China 3 years ago. The product Gendicine is produced by SiBiono Corp. of Beijing, China. It was tested for head and neck cancer and it was approved after only 3 years of testing. It is now being used to treat other cancers as well. Some doctors in China view it as a scientific breakthrough comparable in importance to the discovery of penicillin. Cancer patients are now visiting China to get this therapy and SiBiono has recently started licensing it to cancer centers outside of China.

Dr. Peng Zhaohui who founded SiBiono was trained in the United States and I suspect he brought back to China information on this therapy that was developed in the United States. I think we have reason to be concerned about our country falling behind other nations in the development and use of new therapies. This is caus-

ing economic harm to our country as well as deficiencies in our treatment of critically ill patients.

"This is a wake-up call to America" said Mark Kay, president of the American Society of Gene Therapy and Director of The Stanford University School of Medicine. "We need to look at some of the regulatory hurdles, and the funding issues right now, funding for biomedical research is really hurting, and it's short sighted to think this doesn't hurt our economy in the long run."

I know from your opening statements at your confirmation hearing that you well understand the importance of the FDA and its need for strong and permanent leadership. I am looking forward to your taking on that role and in your leading the FDA in finding ways to streamline its regulatory processes to make them more efficient and to respond to the opportunities and challenges of science and technology.

We hope that the Senate will promptly approve your appointment.

Sincerely,

CHARLES A. REINWALD,
President.

The CHAIRMAN. I thank both nominees for their willingness to serve, and for their attendance and attention today.

I would now turn to Senator Kennedy for purposes of his opening statement.

OPENING STATEMENT OF SENATOR KENNEDY

Senator KENNEDY. Thank you very much, Mr. Chairman. And thank you for having these hearings.

Just, sort of, to frame this hearing, particularly with regards to the head of the FDA, the Food and Drug Administration is perhaps the most important health Agency that we have in the United States of America, and probably in the world. Centers for Disease Control may be a close-to-second. Obviously, NIH has an extraordinary role to play. But the Food and Drug Administration, as you appropriately pointed out, has such influence and responsibility to the American families, in terms of its leadership.

I really deplore the fact that we have not had a permanent chair for that Agency—only 18 months out of the last 5 years—and an acting head cannot do the job and make the difficult judgments and decisions. And we have seen an Agency that's in trouble. That is why we have to give very, very careful consideration. We have a number of important policy issues today to examine with the nominee.

But this Agency is really in trouble, and some would even say, in crisis. At a time, we are on the brink of the life-science century—life-science century, with all the possibilities that this has, in terms of new drugs, and the possibilities of using the information technology that you and I have talked about that can bring drugs onto the market faster—but we need to have an Agency that has the support of an administration, that has the support of the Congress, and is going to follow the—wherever the science is going to lead it. So, this is an important, extremely important, hearing and I welcome this.

I welcome these nominees, Dr. von Eschenbach and Mr. DeCamp, and congratulate them on receiving their nominations. These are two positions worthy of the serious consideration, and we are looking forward to the course of the hearings.

I've always been a strong supporter of the Cancer Institute. I admire Dr. von Eschenbach's leadership there, especially on issues on

genomics and nanotechnology. As a survivor of cancer himself, and physician for patients with cancer, he has brought an important patient-centered perspective to the Institute, and he'll bring it to the Food and Drug Administration, as well.

In the controversies over antidepressants and suicide behavior in children, the withdrawal of Vioxx, the Agency's refusal to approve the sale of Plan B over-the-counter, we've seen the FDA struggling with difficult scientific questions, inadequate resources and authority, and unfair pressures to ignore science. FDA needs a strong commissioner to deal with these and other issues, to refocus the Agency, enable it to make decisions based solely on science, developed after an open and unencumbered scientific debate, not on ideology or political expediency. So, the pending decision on the Plan B is a test case of the FDA's integrity.

Yesterday, Dr. von Eschenbach announced that FDA would not pursue the rulemaking the administration had previously claimed was needed to respond to this application in favor of a more informal negotiation with the manufacturer. If this step leads to a swift and clear decision, I applaud it, but we must make certain that the administration does not use it as yet another delaying tactic.

Serious concerns have been raised about the degree to which political pressures influence FDA's actions on Plan B, and I urge Dr. von Eschenbach to use the upcoming negotiations to begin to allay those concerns, and not to raise them anew.

Sadly, Plan B is not the only example in which the Administration has pressured FDA to value political consideration over the statutes under which it operates and the science before it. Recent survey of the Union of Concerned Scientists presents serious evidence of problems at the Agency. The majority of the Agency's scientists who responded disagreed, or strongly disagreed, that FDA's leadership consistently stands behind scientific staff or managers who propose science-supported decisions, even though they may be politically controversial.

FDA has long been regarded as the gold standard in regulatory work, but that will continue to be the case only if it makes independent science-based decisions in both fact and appearance.

Under Dr. von Eschenbach's leadership, we expect FDA to make decisions solely on the basis of science and in the best interest of the public health. I hope he will assure us that FDA management will no longer reject the views of Agency scientists or actively discourage them from voicing their concern.

Next year will be an important year for the FDA. Four reauthorizations will come before this committee. We'll need the Agency's assistance to enact them. Senator Enzi and I are preparing to introduce a drug safety bill, which will require the Agency and companies to develop a strategy to consider the post-approval safety of a drug. And I hope we'll have Dr. von Eschenbach's support for that effort and the support of all at the Agency.

We also have the opportunity to consider another nomination, Paul DeCamp, to be Administrator of the Wage and Hour Division, Department of Labor. This vital position is charged with enforcing many of our most critical worker protections, including minimum wage, overtime, child labor protections, Fair Labor Standards Act,

the leave requirements, family and medical leave, the prevailing wage requirements, the Davis-Bacon Act, and Service Contract Act.

The actions of the Wage and Hour Administrator affect the lives of every worker in America. It ensures that men and women who work overtime will be able to rely on overtime pay to make ends meet. He protects working teenagers from being forced to use dangerous equipment that can threaten their health or safety. He ensures that parents who need to care for sick children can meet their family needs and still return to their jobs. He defends vulnerable employees, such as migrant workers and day laborers, when they are exploited by unscrupulous employers.

Unfortunately, this administration has showed a troubling lack of commitment to protecting workers' rights in these areas. They've adopted regulations that could deny overtime rights for as many as 6 million workers. They've made sweetheart deals that let repeat offenders, like Wal-Mart, off the hook for violating child labor laws year after year, and they've refused to raise the minimum wage for hardworking people living below the poverty line. And they've failed to protect the rights of hardworking men and women rebuilding the Gulf Coast.

So, the nomination of Mr. DeCamp raises troubling questions. His record clearly demonstrates—question whether—his real commitment to workers' rights, which is necessary to fulfill these important laws. His extensive record of publication shows—does not support the goals of the statute, in many of the statutes he'll be responsible for enforcing. He's advocated change in current law to drastically reduce the number of employees entitled to overtime pay, and suggested that those who work overtime, but are denied overtime pay by their employers, do not deserve the remedies these laws provide. So, his record in the private practice is equally disturbing. And we're very concerned about the alarming number of men and women in the Gulf Coast area who were not paid, and the working conditions they had there, which was a part of the responsibility that he had when he was in the Department.

So, I look forward to those questions, and I thank the Chair.

The CHAIRMAN. Thank you, Senator Kennedy.

Senator Kennedy and I would join in welcoming Dr. von Eschenbach's wife, Madelyn, who's here with us today. Would you—thank you. And I would mention that Mr. DeCamp's wife gave birth to a baby last week; and so, is at home taking care of that baby. So, we congratulate you.

In a moment, I'll ask Senator Hutchison to take a moment to introduce Dr. Eschenbach. And, following the introductions, we'll hear the testimony of both nominees, beginning with Dr. Eschenbach. After both of the nominees have offered their testimony, we'll begin with the first of two rounds of questions by the members who are present and wish to make inquiry of one or both of the nominees. Should any member have additional questions remaining after the two rounds, these additional questions can be submitted in writing to the nominees after the conclusion of today's hearing. I would ask that that be expeditious. The record will remain open for 10 days.

Senator Hutchison.

STATEMENT OF SENATOR HUTCHISON

Senator HUTCHISON. Thank you very much, Mr. Chairman.

I'm very pleased to introduce my constituent, Dr. Andy von Eschenbach. He is a person that I have known for a long time, and I know he is the highly qualified person that we are looking for in this very important job.

I listened to both the opening statements, and I agree that this is perhaps the most important of our medical agencies, because it not only protects America for the safety and security of our medicines and drugs, but it is also important that we have someone who has practiced in medicine and knows that sometimes we have not kept up with the ability to bring things into the market that could save lives. So, I think that he is the perfect person for this position.

His credentials are impeccable. He served as director of the National Cancer Institute. He is a nationally recognized urologic surgeon, medical educator, and cancer advocate. As you mentioned, Senator Kennedy, he's a cancer survivor. He's a cancer survivor three times, so he really does have the patient viewpoint, which is, I think, so important in someone who is doing research and who would seek this position.

Prior to his nomination and service as director of NCI, he spent 25 years at M.D. Anderson Cancer Center in Houston, one of the leading cancer research and treatment centers in America—and, in fact, in the world. He was executive vice president and chief academic officer there. He led a faculty of nearly 1,000 cancer researchers and clinicians.

At the time of his selection to be National Cancer Institute director, he was president-elect of the American Cancer Society. He has made significant contributions to the scientific literature through more than 2,000 articles, books, and book chapters. Dr. von Eschenbach received the National Healthcare Humanitarian Award from the Patient Advocate Foundation in 2005. In 2004, Friends of Cancer Research presented him its Cancer Leadership Award. And George Washington University presented him its Distinguished Cancer Public Service Award.

Dr. von Eschenbach is a native of Philadelphia. He earned a bachelor of science degree from St. Joseph's University, and his medical degree from Georgetown University School of Medicine in 1967. He completed residencies in general surgery and urology at Pennsylvania Hospital in Philadelphia. He also served in the U.S. Navy as a lieutenant commander in the Medical Corps.

Mr. Chairman and members, I know this man, and I know that if you're looking at qualifications, his are impeccable. If you're looking at experience and how he has served in every job he has held, he is without blemish. I think it is important that we have Senate confirmation of the person holding this very important job in our country, and I hope you will give him the vote for confirmation in the Senate.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you very much. We appreciate your being here and the words that you've shared with us.

I would mention that Mr. Paul DeCamp, the nominee for the position of Wage and Hour Administrator at the Department of

Labor, is currently serving at the Department of Labor in the position of senior policy advisor to the Assistant Secretary of Labor for Employment Standards. Mr. DeCamp is a graduate of Harvard College and Columbia University Law School, and he was both a Harlan Fiske Stone Scholar and editor of the Columbia Law Review. Following his graduation from law school, he served as clerk to Judge Alan E. Norris of the U.S. Court of Appeals of the Sixth Circuit. Following this clerkship and prior to entering his current position at the Department of Labor, Mr. DeCamp was engaged in private legal practice, which concentrated on labor and employment matters with emphasis on wage and hour issues.

On behalf of the committee, I welcome both of you. We'll begin with Dr. von Eschenbach's testimony.

STATEMENT OF ANDREW VON ESCHENBACH, NOMINEE TO BE COMMISSIONER OF FOOD AND DRUGS, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. VON ESCHENBACH. Thank you very much, Mr. Chairman, Senator Kennedy and members of the committee.

I am honored to be here this morning to seek your support for my nomination to be the Commissioner for Food and Drugs, and to lead the Food and Drug Administration.

In the 11 months since President Bush appointed me as Acting Commissioner, I've become acutely aware of the Agency's need for strong and permanent leadership with a commissioner that is not only the choice of the President, but also confirmed by the U.S. Senate.

I appreciate this opportunity to earn your trust and support by sharing my vision for the future of this vitally important public health Agency, by helping you to get to know me better as a person, and by highlighting the experience and dedication that I bring to this important role.

To know me, it is important for me to first introduce a few special people who are here with me today. First and foremost is my first date in the sixth grade, Madelyn, who, 39 years ago, I finally got to agree to become my wife and then the mother of our four children. And she is now Nonna to our five grandchildren and the one who's on the way. You should know that I am blessed by her support, and the support of our family, as I embark on this very important challenge.

I also want to introduce a few key members of FDA's senior leadership who are behind me: Mr. Patrick Ronan, Chief of Staff; Dr. Janet Woodcock, the Deputy Commissioner for Operations; Dr. Scott Gottlieb, Deputy Commissioner for Medical and Scientific Affairs; and Mr. David Boyer, Assistant Commissioner for Legislation. They are representing the center directors and the office directors who lead the FDA, as well as the Agency's over-12,000 incredibly talented and highly trained professionals and staff who epitomize the true meaning of the word "public servant." It is important to know that if I am confirmed, their support and guidance will be my greatest asset in leading the FDA.

My fellow Texan and my friend Senator Hutchison graciously outlined my career as a physician. And as I come before you today reflecting on that career, I am struck by the fact that so much has

changed from my early years in training as a urologic surgeon, to a career at the University of Texas, M.D. Anderson Cancer Center as an oncologist, researcher, and educator, to, 4½ years ago, becoming the director of the National Cancer Institute, and now as the President's nominee to lead the FDA.

I am struck by how much has changed in my life, but, in fact, struck by the fact that one critical element of my life has not changed. When I began my career in medicine, 40 years ago, my singular aspiration was to accept the trust that others placed in me and to use my skills to save their lives and improve their health. Today, as I seek the Senate's confirmation to lead the FDA, I remain as committed as ever to that very simple, but profoundly important, ideal and purpose.

It is emphatically apparent to me that, as Commissioner of FDA, my role, and the FDA's role, has always been, and will always be, no matter how much we change over time, to cherish the trust of patients and the public, and that our every single action, decision, or activity must be directed to preserving their lives and protecting their health.

This year, the FDA celebrates its 100th birthday, and a proud tradition of service, and protecting and promoting public health. As the FDA regulates almost 25 percent of all the products that Americans consume, its talented and dedicated employees continue to set the gold standard that is emulated around the world, but has not been equaled. As a Nation, we are blessed that, because of our Food and Drug Administration, we go to bed each night not worrying about the safety of the food we eat or the effectiveness of the medicines we gave our grandchildren.

This standard of achievement must not change. But the world around us is changing, and the FDA of today is faced with new challenges, and the FDA of tomorrow will encounter incredible opportunities.

During my career as a researcher, I have witnessed exponential progress in science and technology that is revolutionizing our very concepts of health and of disease. But, as a physician, I am also painfully aware that, as we sit here today, we struggle—struggle to make available safe and effective new treatments for life-threatening conditions like cancer, Parkinson's, Alzheimer's, HIV/AIDS, to prepare against the risk of pandemic flu, and to deal with emerging threats to our food safety.

Today, we are faced with unprecedented challenges and unprecedented opportunities across the continuum of discovery, development, and delivery of interventions and products that represent the fruits of a revolution in science and technology, but, more importantly, the solution to many problems that threaten our health and well-being. And central to addressing these challenges and seizing these opportunities is the FDA.

While the Agency's first century was truly remarkable, the FDA of the 21st century must incorporate modern management tools and processes to meet the challenge of today while creating scientific tools and technologies to address the ever-evolving, increasingly complex regulatory issues of the future.

To accomplish this goal, the Agency needs strong permanent leadership and efficient strategic management. I am here asking

for your support of my nomination, because I believe I can provide both.

Let me briefly outline for you the strategic focus for leading this Agency into the 21st century.

FDA is positioned as the critically important bridge between scientific discovery and development of products, and the delivery of those solutions to patients and the public. We can, and must, find ways to integrate new information technologies to streamline our regulatory processes, to make them more efficient, rigorous, and transparent, in order to assure the public we serve of the safety and efficacy of those products.

The FDA of the 21st century must be prepared to respond to new opportunities and challenges presented by science and technology. And, through initiatives like the Critical Path to Personalized Medicine, we are working to approve the tools that we use to more effectively evaluate new products and processes. For example, the use of biomarkers, we will be able to predict, earlier and more accurately, both the safety and the efficacy of drugs, biologics, and devices. This is the pathway that will take us into an era of personalized medicine, where healthcare is tailored to each individual patient, where the safety of medical products is enhanced by our improved understanding of how they interact with different patients and under different conditions.

By enhancing both our internal and external collaborations, we can create synergies and enhanced efficiencies to allow us to better communicate and carry out FDA's critical public health mission. Moving forward, it will not be enough just to do the right thing; we must be committed to doing it in the right way.

Above all, I am committed to maintaining the longstanding traditions and values of an Agency whose processes and decisions are guided by sound science and vigorous analysis of evidence, and are based on the best interests of the patients and the public we serve.

Much work remains to fully equip FDA to face the challenges and seize the opportunities ahead, but I am confident that we are on the right path. And, if confirmed, I believe I can provide the leadership and the management that will guide this important public health agency proudly and effectively into its second century of service.

As a physician, one other thing in my life has not changed. I continue to speak with patients and offer advice and consultation. A few weeks ago, I spoke with a young mother who happened to be celebrating her daughter's birthday when I returned her call. She shared with me that she had had a tumor for which she had already been treated with surgery and with chemotherapy, but the tumor was growing and threatening her life and her hope of being there for her daughter's next birthday. The question she wanted to ask of me was, "Is there anything else?"

Senators and members of the committee, millions of people are asking, "Is there anything else?" Anything else for cancer, Alzheimer's, AIDS, diabetes, avian flu, anything else to protect our food supply, improve nutrition, alleviate obesity, keep our animals healthy and our cosmetics safe? The fact is, there cannot be anything else without the FDA—a modern, efficient, and effective FDA.

I know the FDA is capable of fulfilling its mission to assure hope that one day there will, indeed, be something else. FDA is the Agency that can assure Americans hope. Through strong management and leadership, we have the ability to translate innovations into safe and effective new interventions that protect and promote human health. In this task, the Agency cannot, and will not, fail.

It would be the fulfillment of my aspiration to have your trust, and the trust of the American people, to have the privilege to lead the FDA, to save lives, and to assure the health of our Nation and the world. If confirmed, I look forward to working closely with this committee on the many important issues that we'll address together.

I thank you for the opportunity of coming before you today, and I'm happy to answer any questions the committee may have.

[The prepared statement of Dr. von Eschenbach follows:]

PREPARED STATEMENT OF ANDREW VON ESCHENBACH, M.D.

Mr. Chairman, Senator Kennedy, and members of the committee, I am Dr. Andrew von Eschenbach, and I am honored to be here this morning to seek your support for my confirmation to be Commissioner for Food and Drugs, to lead the Food and Drug Administration. In the 11 months since President Bush appointed me as Acting Commissioner, I have become acutely aware of the Agency's need for strong and permanent leadership with a Commissioner that is not only the choice of the President but also confirmed by the U.S. Senate. I appreciate this opportunity to earn your trust and support by sharing my vision for the future of this vitally important public health agency, by helping you to get to know me better as a person, and by highlighting the experience and dedication I bring to this role.

To know me, it is important for me to introduce a few special people who are here with me today. First and foremost is my first date in the 6th grade, *Madelyn*, who 39 years ago finally agreed to be my wife and mother of our four children—Nonna to our five grandchildren and one on the way—you should know that I am blessed by her support and the support of our family as I embark upon this challenge.

I want to introduce a few key members of FDA's senior leadership:

- Mr. Patrick Ronan, Chief of Staff;
- Dr. Janet Woodcock, Deputy Commissioner for Operations;
- Dr. Scott Gottlieb, Deputy Commissioner for Medical and Scientific Affairs; and
- Mr. David Boyer, Assistant Commissioner for Legislation.

They are representing the Center Directors and Office Directors who lead the FDA as well as the Agency's workforce of over 12,000 incredibly talented and highly trained professionals and staff who epitomize the true meaning of the word public servant. It is important for everyone to know that if confirmed, their support and guidance will be my greatest asset in leading the FDA.

My fellow Texan and my friend Senator Hutchison graciously outlined my career as a physician, and as I come before you today, reflecting on that career, I am struck by the fact that so much has changed—from my early years training as a urologic surgeon, to a career at the University of Texas M.D. Anderson Cancer Center as an oncologist, researcher and educator, to 4½ years ago becoming the Director of the National Cancer Institute, and now as the President's nominee to lead the FDA. I am struck by how much has changed in my life, but in fact one critical element in my life has not changed.

When I began my career in medicine 40 years ago, my singular aspiration was to accept the trust that others placed in me to use my skills to save their lives and improve their health.

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During my career as a researcher I have witnessed exponential progress in science and technology that is revolutionizing our very concepts of health and disease. But, as a physician, I am also painfully aware that as we sit here today, we struggle to make available safe and effective new treatments for life threatening conditions like cancer, Parkinson's, Alzheimer's and HIV/AIDS, to prepare against the risk of pandemic flu and to deal with emerging threats to food safety.

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The FDA of the 21st Century must be prepared to respond to the new opportunities and challenges of science and technology. Through initiatives like Critical Path and Personalized Medicine, we are working to improve the tools we use, to more effectively evaluate new products and processes. For example, through the use of biomarkers, we will be able to predict, earlier and more accurately, both the safety, as well as efficacy, of drugs, biologics and devices.

This is the pathway that will take us into the era of personalized medicine, where health care is tailored to each individual patient, and where the safety of medical products is enhanced by our improved understanding of how they interact with different patients, different drugs, and under different conditions.

By enhancing both our internal and external collaboration, we can create synergies and enhanced efficiencies to allow us to better communicate and carry out FDA's critical public health mission. Moving forward, it won't be enough just to do the right thing—we must be committed to doing it in the right way.

Above all, I am committed to maintaining the long-standing traditions and values of an Agency whose processes and decisions are guided by sound science and vigorous analysis of evidence and based on the best interests of the patients and public we serve.

Much work remains to fully equip FDA to face the challenges and seize the opportunities ahead, but I am confident that we are on the right path. And if confirmed, I believe I can provide the leadership and management that will guide this important public health agency proudly and effectively into its second century of service.

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Again, thank you for the opportunity to come before you today. I'm happy to answer any questions the committee may have.

The CHAIRMAN. Thank you, Doctor.

The committee will now hear the testimony of Mr. DeCamp.

STATEMENT OF PAUL DeCAMP, NOMINEE TO BE THE ADMINISTRATOR OF THE WAGE AND HOUR DIVISION, DEPARTMENT OF LABOR

Mr. DECAMP. Mr. Chairman, Senator Kennedy, distinguished members of the committee, thank you for the opportunity to appear before you today to discuss my nomination to be the Administrator of the Department of Labor's Wage and Hour Division. I am humbled and honored to have been nominated by the President for this position.

The Wage and Hour Division enforces some of our Nation's most important and broadly applicable laws, including the Fair Labor Standards Act, the Family and Medical Leave Act, the Migrant and Seasonal Agricultural Worker Protection Act, the Davis-Bacon Act, and the Service Contract Act, as well as dozens of other statutes. At its core, every law that the Wage and Hour Division enforces is about protecting workers. These laws apply to approximately 130 million employees, and they benefit the countless millions more who are the family members.

I believe that my background has given me an inherent empathy for all working Americans. I grew up in a small town in southeastern Massachusetts. People in my town tended to work in trades, textiles, jewelry fabrication, and other predominantly blue-collar occupations. I attended public schools from kindergarten through high school. My father, who was not a college graduate, spent most of his working life as a night watchman, relying on every cent of his shift premium and his overtime pay just to make ends meet. My mother lost her job, due to company downsizing, after 15 years of service.

I have personally worked in a number of jobs. I have had the experience of punching time clocks, working for minimum wage and overtime, and pulling double shifts. I have washed dishes, bussed tables, mopped floors, stocked shelves, de-iced freezers, flipped burgers, gotten splashed by fryolator grease, run a cash register, and more. I spent years working side by side with people who needed these jobs to support their families. Most recently, my wife is currently on leave under the Family and Medical Leave Act. Our second child, William Charles DeCamp, was born a week ago today.

I respect working men and women, as well as their families. I respect the right of youth to work in a safe environment. I under-

stand and empathize with people who are economically vulnerable. I appreciate how what may seem like small amounts of money by Washington, DC., standards—$20 here or $100 there—can, for a great many families, make all the difference between paying the rent, or not; making the car payment, or not; being able to afford food and clothing, or not.

I would consider it a genuine honor and privilege to serve as Administrator so that I can protect workers like my parents, the people I grew up with, and the many millions of Americans like them throughout the Nation who depend on the Federal wage and hour laws to ensure that they get a fair day's pay for a fair day's work.

In my career as an attorney, I have gained useful insights into how wage and hour issues play out in the workplace, including how employers formulate workplace policies, how violations occur, and how disputes develop. I believe that most employers intend to comply with the law, and that many wage and hour violations result from an employer's good-faith misunderstanding or lack of knowledge of what the law requires. At the same time, I appreciate the importance of obeying the law and securing any appropriate remedies for workers whose rights have been violated, even inadvertently.

In my view, the primary goal for the Wage and Hour Division is to achieve maximum compliance with the law. If I am confirmed, I would pursue that goal in a number of ways.

First, the Wage and Hour Division must promptly process and investigate complaints it receives alleging violations of law. That activity accounts for most of the Agency's enforcement work, and I would continue to emphasize that aspect of its operations.

Second, I would continue, and increase, directed enforcement efforts that focus on protecting the rights of the Nation's most vulnerable workers, such as children, employees in low-wage industries, migrant workers, and undocumented individuals. I would work closely with field personnel to identify specific areas, whether types of claims, specific industries, geographic regions, or particular employers, where the Agency believes that violations are going unreported or under-reported. In such instances, it may be appropriate to supplement the Agency's complaint-based enforcement activities with directed investigations, and that work may differ from region to region.

Third, I would make it a priority to review and to update the child labor regulations. Those regulations have not been substantially revised in approximately three decades. I believe those regulations should reflect current information regarding the risks posed to minors in employment. These measures would be in addition to the actions necessary to respond to broader challenges that may arise, such as protecting workers in the Gulf Coast region in the aftermath of Hurricane Katrina, addressing the needs of day laborers, and safeguarding reforestation workers.

I believe in our wage and hour laws and the essential purposes they serve. I know how important these laws are to the individuals and families whom the laws protect. If I am confirmed, I will do my best to enforce those laws justly, fairly, and vigorously.

Mr. Chairman, this concludes my prepared remarks. I will be happy to answer any questions you or the members of the committee may have.

[The prepared statement of Mr. DeCamp follows:]

PREPARED STATEMENT OF PAUL DECAMP

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Mr. Chairman, this concludes my prepared remarks. I will be happy to answer any questions you or the members of the committee may have.

The CHAIRMAN. Thank you very much.

I appreciate the testimony of both of you. I'll begin with a question for Dr. von Eschenbach.

The most important part of your job will be making decisions. And I appreciate, in your testimony, where you briefly explained how you go about making a decision, and what it would be based on.

Now, in light of your testimony, I'd like to explore how you made the decision that you just made on Plan B. Yesterday, you announced that remaining issues could likely be worked out within a few weeks. Your predecessor said the Plan B application raised complex legal and regulatory questions, and he directed the FDA to issue an advance notice of proposed rulemaking. He received tens of thousands of comments in response to the notice. Yesterday, in your letter to the sponsor, you indicated that the comments suggested there was no need for rulemaking. If the FDA's authority was, indeed, unclear, as the Agency suggested in its notice, is it clear now? How did the comments inform your decision? And what new information did they add to the discussion? And, finally, why did you make the announcement yesterday, the day before the confirmation hearing?

Dr. VON ESCHENBACH. Thank you, Mr. Chairman. I will attempt to answer each of those points. And perhaps, with your permission, it might be helpful to do so if I just frame the issue as I encountered it, and some of the background that's associated with it.

When I arrived at the FDA, approximately 11 months ago, this was, of course, a process that had already been underway. It began in April 2003, when the manufacturer of this particular product applied for a switch from it being available by prescription to being available without prescription.

This particular drug is a contraceptive, an oral contraceptive, that is used for emergency purposes, not for routine purposes, and it acts by preventing conception. It had been used by prescription, across all age groups of women. Now it was being requested to be applied to all age groups of women without the need for a prescription. And, under those circumstances, the issue that the FDA was addressing was whether it could be used safely, and whether it could be used appropriately, without the need for medical supervision.

The decision that was ultimately arrived at by the Center director in reviewing and coming to a decision was that there was a sub-

set of women, young girls in their teenage years, in whom it was not clear that this could, in fact, be used without the need for medical supervision. And, on that basis, the application was denied. And the company submitted an amended application in which they bifurcated the ability to dispense this drug by providing it for over-the-counter, or without prescription, if you will, for women who were older than 16, and by prescription for those who were 16 and younger. This created, for the Agency, a new question with regard to the regulatory framework, a question independent of the review of the application, per se, but having to do with the issue of being able to appropriately provide access to a drug that would be both by prescription and nonprescription, when the drug was in the exact same formulation, in the exact same dose, in the exact same packaging, and how that could be managed appropriately and still protect and preserve public health.

On that basis, my predecessor believed that we needed to move to a process of an advance notice for a proposed rulemaking in which that process would allow that question to be open to a wide range of opinions that would inform the Agency with regard to whether it would or would not need to go forward with separate rulemaking to address that issue of something being nonprescription and prescription at the same time. That is the process as it existed at the time that I came to the FDA.

My commitment, at that point, in carrying through on that process, was to, first and foremost, address the issue of the process, the mechanism that had been put in place for the advanced notice for proposed rulemaking. The public commentary came to a close in November. There were approximately 47,000 comments to the record. They were able to be, then, processed and categorized in a way that addressed the various questions that were posed to the Agency. Those responses, and that input, was analyzed with an internal process. I engaged in the analysis of that, and the examination of the evidence. And it was the conclusion of career staff, and I concurred in that conclusion, that the overwhelming evidence that came out of that process indicated we did not need to move forward with a special process of rulemaking, that we could accommodate the bifurcation of this application within our current regulatory framework.

Based on that decision, and the fact that I could remove the need for rulemaking, I turned my attention back to the application itself, and, as you indicated, I informed the company, yesterday, that we were prepared to engage with them in a discussion of going forward with consideration of their application if we could arrive at an agreement in which we could move forward and allow the drug to be available by nonprescription for women who are 18 years of age and older, and with prescription for those who are less than 18 years of age, and with a risk-management plan that would assure, and be certain, that young girls who are in need of medical supervision if they are going to use this particular emergency intervention safely and appropriately, I was willing to move forward with a final decision on their application. And so, I made a decision to not go forward with rulemaking, and I made a decision to engage with the company to work through an adequate risk-manage-

ment plan that would then lead to a final decision on their application.

And the reason it was done yesterday is that this has been a process that has been unfolding and has been underway, and, by virtue of the legal prescriptions and requirements, I could not disclose or make public any of these discussions until I first notified the company of my decision, and that occurred yesterday morning.

The CHAIRMAN. My time has expired.

Senator Kennedy.

Senator KENNEDY. The unfolding underway is, I think, the understatement. Let me just go through—because I think we're going to have questions in this area, and I think you've given us an overview on it. Just very quickly, as you remember, Doctor, you had—December 16, 2003, FDA Science Advisory voted 24 to 3 to support approval of Plan B for over-the-counter use. And, on February 22, 2004, FDA was required by law to issue a decision, failed to meet the deadline. July 21, 2004, response FDA, belated rejection of its initial application. The manufacturer modified the application to address the FDA's concerns. Then, in January 2005, FDA failed to meet the statutory deadline for acting on the revised application. Then, July 2005, Secretary Leavitt committed to taking action on the application by September 1, but the only action the FDA took was to say it needed more time to study the application. Then, on November 15, 2005, GAO issued a report stating,

> "In the decade from 1994 to 2004, only one application for a drug to go OTC, over-the-counter, that was rejected after the Advisory Committee voted for approval, and that case was Plan B."

So then, yesterday, the administration issued not a decision, but a framework.

Now, you have that background, plus the background that says that the changing of the date of the individual women, the Agency reviews the data and says that it can be approved if the company files an amendment for women 16 and up. Then the company does so, and the Agency says, "Actually, we need to make the application for 17 and up." And then, a year later, it says, "No, it has to be 18 and up."

So, there's a number of issues and questions. First, the question to you is, When can the American people, at least, expect the FDA to decide what the science says about Plan B? Will it be next week or next month or next year? We'll have to wait until the future on that issue. And then, second, nearly 3½ years—this is the broader issue—and that is, 3½ years after the application, FDA hasn't made a decision, one way or another, and moved the goal posts. And what's your reaction to those that say that this kind of a process really makes it basically unacceptable, in terms of approving, you know, new drugs? What message does that say?

Granted, these are all prior to the time—you know, that you're familiar with this issue, so we—put it in that context. What's it say about the process? And then, when do we—are we going to get the actions?

Dr. VON ESCHENBACH. Senator, if I can just address that, and I'll attempt to do it succinctly, but I need to compartmentalize this very complex issue into some parts.

With regard to the initial application and the difference of opinion that occurred with regard to the scientific review and the Advisory Committee recommendation, I completely concur with the decision that was made at that time by the director of the Center for Drug Evaluation and Research. In looking at that data, although in—overall, across all age groups, the data indicated that this drug could be used properly and safely in a nonprescription form, that data did not apply equally to all of the subsets of women within that study. And, in fact, the amount of data and information that was available for young girls, who were 12, 13, 14, 15 years of age, was really inadequate in which to draw a decision. And, because of the concern about not being able to understand how to use this emergency contraceptive properly, and because of the concern that without medical supervision in abuse that would, in fact, create safety issues or concerns, as compared to older, adult women who are more mature and able to make decisions, he did not move forward with the approval of that application. And I concur with that decision.

That resulted, then, in the reapplication by the company with regard to this bifurcation of prescription versus nonprescription. And that opened up a different set of questions.

Senator KENNEDY. I don't want to interrupt, but I will, just on this point, quickly, because my time is up. The GAO report says that there are no age-related marketing restrictions for safety reasons for any of the prescriptions of OTC that FDA has approved. I don't know whether you're familiar with that finding that they had in there. It was just related to your comment.

Dr. VON ESCHENBACH. I——

Senator KENNEDY. I'm——

Dr. VON ESCHENBACH. I apologize. I'll——

Senator KENNEDY. No, that's okay.

Dr. VON ESCHENBACH [continuing]. Be more succinct.

Senator KENNEDY. Do you want to just continue——

Dr. VON ESCHENBACH. Well, I—to that point, what I hope to rapidly communicate is the fact that there are issues related to age within this group, and what the advance notice for proposed rulemaking commentary provided was additional information that made it possible to make a decision now that couldn't be made when that first came before the FDA, when the company amended their application.

Senator KENNEDY. Thank you.

My time's up, Mr. Chairman.

The CHAIRMAN. Senator Isakson.

Senator ISAKSON. Dr. von Eschenbach, I don't often have the occasion to make a decision on someone having had experience in working with them, but, in your case, I do. And I thought I would open my questions, really, with a statement for you to respond to.

About, I guess it was 9 months ago, or very shortly after you became Acting Commissioner, an incident came up—three incidents came up with regard to Tysabri. And the decision was made to pull that drug off the market. For the edification of the people here, Tysabri is a breakthrough drug for multiple sclerosis that had had remarkable success, and was actually bettering the lives of many people who felt like their life was about gone.

Because of a doctor in Atlanta, and because of friends of mine who suffer from MS, I had a working knowledge of the benefits, and had seen, firsthand, those benefits. And when the FDA pulled the drug off, because of three particular incidents of death, it concerned me greatly, and it concerned them greatly, because, for them, the only way to stay alive was Tysabri.

I brought this to your attention. And if my recollection is clear, in less than 4 months, maybe 5 months, you and the Agency worked through all the research you had to do, and Tysabri is now back on the market, with particular protocols for the physicians and the patients.

My understanding is that that was a record time for the FDA to respond in such an incident. So, I want to, first of all, say thank you, on behalf of thousands of MS patients in the United States, for your quick response. And, second, have you addressed that particular process?

Dr. VON ESCHENBACH. Thank you very much, Senator.

And I think your question points out the principle that guided that decision, as well as the one we have just been discussing, and that is to find that correct balance between protecting and promoting public health.

In the case of Tysabri, the deaths that occurred were totally unexpected, and had not been anticipated as to be associated with that particular drug. And in order to protect the public health, the drug was voluntarily withdrawn until we could get additional information and until we could put in place processes that would then allow us to reintroduce that drug to provide that lifesaving intervention for those unfortunate patients with multiple sclerosis, while, at the same time, having safeguards in place that could then assure their protection, as well. Once we arrived at that point, and working judiciously because of the severe problem that MS presents, we were able to arrive at a place where we believe now, it's back on the market with restraints and constraints that protect health, while also providing lifesaving intervention. And that principle and that process will guide all of the decisions that we make at FDA.

Senator ISAKSON. Well, again, I want to thank you on behalf of those people that suffer with MS that are benefiting from the prescription of the Tysabri, and thank you for your swift action as Acting Commissioner.

Just so Mr. DeCamp doesn't go to sleep when everybody's talking about Plan B and asking you questions, I probably ought to ask Mr. DeCamp a question. Are you an attorney, sir?

Mr. DECAMP. Yes, I am, Senator.

Senator ISAKSON. I did not get to read everything. What was your most recent private-sector responsibility as attorney? What type of an attorney were you?

Mr. DECAMP. I worked as "of counsel" with Gibson, Dunn & Crutcher, focusing on labor and employment law and appellate matters, with an emphasis on wage and hour work.

Senator ISAKSON. Very good. Are you familiar with the Senate version of the immigration reform bill that passed the Senate?

Mr. DECAMP. I have not reviewed the legislation yet. I've read what's in the papers about it.

Senator ISAKSON. OK. Well, at some point in time—I'm not going to put you on the spot, then, but I would like, if I can, Mr. Chairman, to ask you to—I'll send you a formal request, but I think the issues over the application of Davis-Bacon and the Senate immigration bill that passed raises significant questions in terms of a reach of its application beyond its original intent, and I'd like to know—from your standpoint as a labor lawyer, and from your professional opinion—what you think of that. So, I'll submit that to you in writing, rather than catch you having not read it and then try and get you to make a decision. But I would like to have your input on that.

Mr. DECAMP. Yes, Senator.

[Editors Note: The information previously referred to was not available at time of print.]

Senator ISAKSON. That's all I have, Mr. Chairman.

The CHAIRMAN. Thank you. As you can tell, I'm following the past practice of hearing from those that are here at the sound of the gavel, then by arrival following that. So, Senator Mikulski, you'd be next.

Senator MIKULSKI. Mr. Chairman, did you say in how we arrived, or by seniority?

The CHAIRMAN. It's by how you arrived at the sound of the gavel and then after.

Senator MIKULSKI. I think my colleagues at the other——

The CHAIRMAN. I——

Senator MIKULSKI. First of all, I'd love to have my time now, but—

[Laughter.]

The CHAIRMAN [continuing]. I thought——

Senator MIKULSKI [continuing]. But I don't want to——

The CHAIRMAN [continuing]. I thought the four of you——

Senator MIKULSKI [continuing]. Go in front of my colleagues.

The CHAIRMAN [continuing]. Were here at the sound of the gavel.

Senator MURRAY. We always cede to our Senator Mikulski.

[Laughter.]

Senator MIKULSKI. Well, then, thank you very much, Mr. Chairman.

And my question goes to the fact that I sit here as the very proud and enthusiastic Senator representing FDA. FDA is in my State. And there is over 10,000 very, very earnest and dedicated employees, and, over the years, who have fought for working on a bipartisan basis, the right facilities for these employees, working with Senator Hatch to make sure that employees that were working in 39 different spots, some converted hotel/motel rooms, could be in—consolidated at a realigned military base—and we've done that on a bipartisan basis—worked to create, on a bipartisan basis, the Office of Woman's Health with Senator Snowe, and also to be able to support the employees. But, Dr. Eschenbach, as I spoke to you yesterday and before, FDA's in crisis. There is a crisis of morale, there is now a crisis of confidence in the reliability of FDA decisions, there is a crisis about are there the scientists operating under a gag rule, putting politics above science, and there is a crisis ensuring the reliability and the safety of our drugs.

My questions today to you are, while your—you have a compelling personal narrative and a compelling background of professionalism and competence, but we need plans, and we need commitments. If one looks at where we are now—let's just take the issue of morale. There are—the Union of Concerned Scientists have surveyed FDA and said the scientists are hemorrhaging, they're leaving your agency, because they don't know if they have a future where they can put their talents together, there are over 100 whistleblower cases pending from your agency, 100 scientific whistleblower cases. What do you intend to do about the morale? And, No. 2, do I have your commitment that you will not politicize the scientific decisions at FDA? And what would be your plans for doing so?

Dr. VON ESCHENBACH. Thank you very much, Senator.

And I would like to address this issue of morale by first thanking you and Senator Hatch, as well as other Members of the Congress, for the tremendous support of the White Oak consolidation for FDA, because, although that—views possess important——

Senator MIKULSKI. I only have a very few minutes, let's get to the answers. You can thank me later.

[Laughter.]

Dr. VON ESCHENBACH. Well, the issue there is, it's a morale improvement to bring the Agency together for greater integration and sharing, which is one of my strategies. Second, within that integration and sharing, to create the climate for vigorous scientific debate in which, when there is a difference of opinion, we have in place guidances and processes for refutation, including an ombudsman process, so that we can surface that difference of opinion and not have that become an issue in which people fear that they will be penalized for voicing that opinion appropriately within the context of that vigorous scientific debate.

Attention to our workforce is my No. 1 priority. It is the most precious asset that FDA has. And improving and enhancing retention and recruitment opportunities, career-development opportunities, will also address morale.

Senator MIKULSKI. Let's come back to the concern about being stifled and under a gag rule for presenting views. Would you consider establishing, kind of, a back-channel, dissent channel, where employees who have concern that perhaps mid-level people, or even political employees at FDA, would be unduly exercising improper influence, and that you would have a dissent channel that would come directly to you, or so that you would be aware of what they say and what their concerns would be, so that they could be properly addressed?

Dr. VON ESCHENBACH. Yes, Senator, I would. And that is parallel with the experience that I had, as Senator Hutchison alluded to, in being the chief academic officer at a very large, complex academic institution where that kind of scientific debate and difference of opinion is part and parcel of what we do. And to allow a mechanism for adjudication of differences, to allow, where there are grievances and concerns about the process, to have a pathway forward to the senior leadership and to, in fact, I——

Senator MIKULSKI. So, what I'm suggesting——

Dr. VON ESCHENBACH [continuing]. Would be there.

Senator MIKULSKI [continuing]. Is not in lieu of the normal personnel adjudication, but it's often too slow and too frustrating.

Let me, then, get to drug safety. Your predecessor did not see the need for an independent drug-safety board, yet Senator Grassley, myself, Senator Dodd, others, feel that they should. You're familiar with the cases, the antidepressants around children, there was—Andrew Mosholder raised flashing yellow lights, they were ignored—the Vioxx issue, the Ketek issue, the defibrillator issue. So, my question to you is, What do you—and when I talked to Dr. Crawford, he said he was going to have a board, but it wasn't going to report directly to him, because it dealt with personnel and budget, and he didn't think that was his job. I was a little surprised at that. How do you intend to ensure—what would you see, the way of ensuring drug safety, and also the safety of medical devices that are so important and are part of our innovation economy? What mechanisms would you see? And do you see the need for new legislation? Or do you believe you can do this with the administrative authority that you have?

Dr. VON ESCHENBACH. I believe I can accomplish this with the administrative authority I currently have, to put in place a system that would include the incorporation of principles in critical path that have tools, scientific tools, to be able to determine safety of these new products and interventions before they are ever introduced into patients, to have processes internally within our review mechanisms, based on the modern information technology where we can——

Senator MIKULSKI. Well, what do you see? Do you see a drug safety board within FDA, or do you see one outside of FDA?

Dr. VON ESCHENBACH. I see using the current mechanisms that are already present within FDA, including the fact that we have a drug safety board, that includes other members outside of the FDA, within the Federal Government, who can engage in these confidential discussions and really provide some additional oversight. And then, once the drug is approved, we need to continue that safety——

Senator MIKULSKI. Well, that's the post-marketing issue, but there's been a GAO report on postmarketing that talks about the Office of New Drugs and the Office of Drug Safety. And the GAO found it woefully lacking. You see, our concern is that what is now at FDA hasn't been working. Now, this is not a hearing to fingerpoint, it is the hearing to pinpoint that. And I really don't know if FDA is capable of having a board within itself. I really don't know. All I'm interested in is that we be the gold standard for not only our own country; it's what you and I talked about on the phone.

Dr. VON ESCHENBACH. Yes.

Senator MIKULSKI. All over the world, there are people that are going to take drugs that were invented in America, and they've got to know that it's okay.

Dr. VON ESCHENBACH. Well, what I'd like to assure you of, Senator, is, this is my highest priority, and it will not be one thing, but it will be a number of things that I am committed to do to bring the Agency on a modern basis of management and infrastructure that'll enable us to address the issue of safety in multiple

ways and in multiple parts and components. The integration, I talked to earlier. And so, this will be a systemic—or a systematic approach to safety that's going to be comprehensive, and I'm absolutely committed to it, as you are.

Senator MIKULSKI. Is my time up?

The CHAIRMAN. Thank you.

Senator Hatch.

Senator HATCH. Well, thank you, Mr. Chairman.

Mr. DeCamp, you're—I'm not going to ask you any questions—you're certainly highly qualified, and—I've looked at your resume and your background, and you certainly have all that it takes to do this job, and more, in my opinion.

Dr. von Eschenbach, you're one of my favorite people. There's no question that you have the qualifications to be FDA head. It was well over a decade ago when we passed the FDA Revitalization Act to create the White Oak campus, and I am so grateful to Senator Mikulski and others on this committee and throughout the Congress for working with us to get that finally up and running. But let me just ask you this. When is the completion of the campus expected? And how much money is it going to cost?

Dr. VON ESCHENBACH. I cannot give you at this moment, Senator, the final cost. And I'm anticipating that opening—completion will be occurring around 2011–2012.

Senator HATCH. See, if we had done that right off the bat, it would have been completed by now. And, of course, we wouldn't have these 39 different locations, with supervisors traveling in between and losing all that time and efficiency.

Dr. VON ESCHENBACH. I would comment, Senator, that GSA has been extraordinarily cooperative and is working extremely hard in—to keep that on a very accelerated——

Senator HATCH. I don't blame——

Dr. VON ESCHENBACH [continuing]. Timeline.

Senator HATCH [continuing]. GSA. I blame us, up here. I think we didn't put the funds up, when we should have done that. I agree with Senator Kennedy, this is one of the most important agencies in any government anywhere. The health of our people depends a great deal on what you do.

Ten years ago, the Dietary Supplemental, Health, and Education Act authorized the FDA to develop GMPs, or good manufacturing practice standards, specific to dietary supplements. And I recognize that the law did not require you to do so, but it did allow this process to begin. And we were greatly heartened that FDA began to develop dietary supplement GMPs. Now, that's the good news.

The bad news is that somewhere over 10 years ago, DSHEA authorized the FDA to develop GMPs for dietary supplements, and we have not yet seen them published. Now, it's my understanding that the HHS-approved GMP regs were forwarded to OMB for final clearance during the Clinton administration. And shortly after President Bush was elected, my office received a call from a senior HHS official stating that HHS is going to make certain that GMP regulations 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've had

numerous reports that the regulations were going forward, but they still have not been published.

Accordingly, I'd like to know the following about the status of these regulations. Have they been cleared in final form by the FDA? Have they been cleared in final form by HHS? What specific issues remain outstanding so that these regulations may be finalized, if they haven't? And when will the regulations be published? What date certain can be—can we be assured that the regulations will have been finalized? Can you tell me a little bit about that?

Dr. VON ESCHENBACH. The regulation has cleared the FDA, Senator, and is at OMB for their analysis and review. FDA is committed to working very closely with OMB about any issues or questions they raise so that we can facilitate this coming to its final conclusion and closure, because, like you, we are very committed to the important role that dietary supplements can play in promoting health and well-being of Americans, and want to assure their safety and the quality of their manufacturing and their labeling so that Americans can use them safely and appropriately.

Senator HATCH. Well, the responsible people in that industry want to have this done, and they want to be able to have the benefits that come from having GMPs guiding them. And I think it's critical that we do that, because we've had an explosion in dietary supplement development and manufacture since the DSHEA was enacted, and it's just really critical that we do that.

Let me just ask one other question, and that is—I wouldn't mind hearing you talk about your goals as FDA Commissioner. And I'd like to know about what you've been thinking your priorities will be as FDA Commissioner. I think that would be helpful to us all.

Dr. VON ESCHENBACH. Well, thank you, Senator.

I think I can most easily describe them as falling into two parts. One, and most important issue at present, is to put the FDA on a modern management infrastructure where I would make certain that we were carrying out our processes and activities in the most efficient and effective way, that we were utilizing our resources with great stewardship, and maximizing their impact. And, at the same time, the other issue is to continue to advance initiatives like the Critical Path for Personalized Medicine, to bring new modern scientific tools and technologies into the regulatory process so that we can address many of the complex issues that are emerging out of these new opportunities.

Senator HATCH. Well, thank you.

Mr. Chairman, I appreciate this time. I appreciate you and Senator Kennedy holding this hearing, and I hope that we can push this nominee through. We need an absolute head at the FDA, and it would mean a lot to, I think, the country, to everybody concerned. And I would appreciate any efforts that all of us here on this committee can make.

The CHAIRMAN. Thank you. And as a former chairman, I always appreciate the careful work that you do in the hearings, as well as prior and after. Thank you.

Senator Murray.

Senator MURRAY. Thank you, Mr. Chairman.

Mr. DeCamp, I do have questions and concerns. I hope that I can get to them. I'm not going to ignore you entirely.

But, Dr. von Eschenbach, let me start by just saying that I echo the concerns of several of my colleagues that have talked about the deep crisis that's in the FDA because of the lack of decisionmaking. We've worked very hard, on this committee, to put in place predictability for consumers, so they know, when they purchase a drug, that it is, based on science, safe and effective; that the scientists themselves who work at FDA know that, when their work is done in a scientific manner, that it will be accepted that way; certainly, for the manufacturers, who spend millions of dollars getting to the point where they've brought a drug to you, know that predictability is going to be based on science.

So, Plan B is, sort of—you're hearing a lot about, and will hear a lot about, because it's symbolic of people's crisis of confidence in the FDA. And how you handle that, and your leadership on that, is truly key to whether or not many of us feel that your nomination should go forward.

Yesterday, you did send out a letter, and I want to ask you about that. I want to—well, let me just ask you. The science is critical. Is Plan B safe and effective for women who are 18-years old? Is——

Dr. VON ESCHENBACH. Plan——

Senator MURRAY [continuing]. Is Plan B safe and effective for women who are 18-years old?

Dr. VON ESCHENBACH [continuing]. Plan B can be used safely and effectively——

Senator MURRAY. For women who are 18, correct? Is it safe and effective for women who are 17?

Dr. VON ESCHENBACH. Plan B can be used, but with medical supervision.

Senator MURRAY. Well——

Dr. VON ESCHENBACH. I believe it could be used appropriately——

Senator MURRAY. I have a letter from your predecessor from August 2005, who says, "The FDA found it safe over-the-counter for women ages 17 and older." Do you disagree with that?

Dr. VON ESCHENBACH. Senator, what I'm trying to communicate to you is, I believe the drug can be used safely and effectively. I believe that there need to be processes in place that reflect the differences——

Senator MURRAY. Well——

Dr. VON ESCHENBACH [continuing]. In age——

Senator MURRAY [continuing]. Let me——

Dr. VON ESCHENBACH [continuing]. So that that can happen.

Senator MURRAY. OK. Last year, FDA found that it was safe and effective for women who are 17 and older. Yesterday, all of a sudden, you send out a letter changing the age from 17 to 18. What new scientific or medical data about safety and effectiveness can you share to justify that change?

Dr. VON ESCHENBACH. That change—that decision is based primarily around our ability to manage this particular drug being both prescription and nonprescription at——

Senator MURRAY. So, there's——

Dr. VON ESCHENBACH [continuing]. The same time.

Senator MURRAY [continuing]. No medical or scientific data.

Dr. VON ESCHENBACH. There's no difference in the drug, medically or scientifically. It's the ability to make sure that it's used safely and appropriately when it's both by prescription and not by prescription.

Senator MURRAY. Well, did—is it safe and effective for women—safe and effective—just asking those questions—science based, for women who are 17 and under?

Dr. VON ESCHENBACH. It is safe and effective, if used appropriately.

Senator MURRAY. But you are holding this drug to a higher standard, and I would like to know where in the FDA's charter it says that FDA should approve drugs based on behavior.

Dr. VON ESCHENBACH. I'm sorry, Senator, I'm not making the decision essentially holding it to a higher standard or based on behavior, I'm holding it to a principle that, in order for the drug to be approved as the application currently exists, I must assure the safety and the protection of the women who will be using it.

Senator MURRAY. Do you have data that shows it cannot be used safety and effectively for women who are 17?

Dr. VON ESCHENBACH. Well, the point of the data that was analyzed, and the decision that was made by the Center director, which I support, was the fact that the data was inadequate to be——

Senator MURRAY. Well, I actually——

Dr. VON ESCHENBACH [continuing]. Absolutely sure.

Senator MURRAY. But the letter that we have says it is—scientific data does show that it, from a year ago, from your agency—that it's safe for 17.

Dr. VON ESCHENBACH. Senator Murray, I've looked at the data, and I've reviewed the decision.

Senator MURRAY. So, you've changed the FDA's decision from a year ago.

Dr. VON ESCHENBACH. I've made the decision, and I am of the opinion that, as had been judged by the Center director, the data was insufficient to be able to assure the safe and effective use of this drug——

Senator MURRAY. You can understand——

Dr. VON ESCHENBACH [continuing]. By young women.

Senator MURRAY [continuing]. I mean, a year ago, it's safe for women who are 17, by your own data, and now, all of a sudden, it's 18. I'm pointing this out, because we need to show scientific data. This is why this is so startling to all of us.

But let me ask you another question, because, as you know, our time's short. I was really surprised yesterday to see that you want to put the burden of enforcement on the manufacturer, and you said that if the manufacturer doesn't meet these standards, the FDA will deny the over-the-counter application for all ages. So, if a pharmacist ignores a warning label, or the manufacturer's instruction, who is to blame? The pharmacist or the manufacturer?

Dr. VON ESCHENBACH. Well, the application is to provide the drug across the continuum, prescription and nonprescription. And, in order to do that, it is my opinion that we must have a proper risk-management plan, which the company did, in fact, submit with its application. And as long as that risk-management plan

assures that we are going to protect the women and young girls who are going to have——

Senator MURRAY. The manufacturers——

Dr. VON ESCHENBACH [continuing]. Access to this drug.

Senator MURRAY [continuing]. Do. I guess that's the question that I am going for, and the concern that I have, that you're basically, in your letter yesterday, telling the manufacturer, if they can't prove themselves—that they can control the pharmacists across the country, that all women will be denied the use of Plan B. And, as we know, Plan B is only effective within a short amount of time, so basically you're saying to women who are 25 and 35 and 45 that they will be denied the use of an effective drug. So, based on a manufacturer, it's a question I raise, because it sort of goes to the whole issue of the crisis of confidence we have in the FDA in making decisions not on behavior, but on science. And that's my concern.

And the second concern is—as you know, we've been down this road before—right before a nominee is to be confirmed, we are told that a decision is imminent. You talked about meeting the manufacturer within the next 7 days. But that's not a decision. That's looking for more information. It is exactly where we were 1 year ago today. And I want to know from you, What is a date certain that you will make a decision, yes or no?

Dr. VON ESCHENBACH. Well, Senator, I hope you'll understand that I view it as yesterday, having made an important decision to not go forward with rulemaking.

Senator MURRAY. To change——

Dr. VON ESCHENBACH. I invite——

Senator MURRAY [continuing]. The age to 18, to ask the manufacturer and then to—what?

Dr. VON ESCHENBACH. And to then invite the manufacturer to come in immediately so that we could address the elements of the risk-management plan. If we can then provide that risk-management plan to assure the safe, appropriate use of this medication, this high dose hormone, both for these young girls, who may not use it appropriately, because the data was inadequate to assure the FDA that that was the case, then we would go forward with——

Senator MURRAY. Is it not——

Dr. VON ESCHENBACH [continuing]. The approval.

Senator MURRAY [continuing]. The case that you can meet them—with the manufacturer and decide to have a 90-day—another—send out opinions and ask people—opinions back again?

Dr. VON ESCHENBACH. It——

Senator MURRAY. You could do that, correct?

Dr. VON ESCHENBACH. It is my intent, Senator, to have the FDA meet with the manufacturer of this drug to address the elements of the risk-management plan so that we could move forward in a way that would provide this drug with greater access——

Senator MURRAY. But you can't give us a date certain.

Dr. VON ESCHENBACH. That date certain depends upon the company and the discussions and negotiations. So, it is not a date I can guarantee; it's a date that, right now, quite frankly, is dependent upon the company coming in and us having these conversations.

Senator MURRAY. The uncertainty is what is causing everyone deep concern. You understand that. And leadership is making decisions. You understand that.

Dr. VON ESCHENBACH. I hope that the facts that I outlined in the letter, which you alluded to, create for the company a very clear, very specific set of issues that they can immediately address, and, if they do so, then this application will move forward.

Senator MURRAY. Mr. Chairman, my time is expired.

The CHAIRMAN. Senator Reed.

Senator REED. Thank you very much, Mr. Chairman.

And, Doctor, I just want to see if I understand, sort of, the logic of the decision. You're creating a break—18 and under, and 18 and above. Is that because there's a different dosage that's required, or a physical evaluation or a—someone under 18-years old?

Dr. VON ESCHENBACH. No, Senator, it's precisely because the drug is exactly the same, regardless of which age group, but the issue of being able to use it safely and appropriately is what has created this question about the bifurcation and where you draw that line. I believe 18 is appropriate. It's consistent with the data. It's consistent with other processes and principles that we use for individuals to be able to make decisions as adult, whether it happens to be alcohol or tobacco or other things that we consume. So, it's a cut point, and we have to have some cut point.

Senator REED. Well—you know, I'm following up on Senator Murray's questioning—last year, there was data, or at least analysis, suggesting 17 was the appropriate age. But what concerns me—and I ask these questions, honestly, to try and understand—it seems like you're saying that certain women might not be capable of administering their drug themselves without supervision. And that seems—18 is sort of an arbitrary construct, if that's the underlying notion. There are some men and women, who are 16 and 17, who are probably more capable of understanding directions on a drug, and following those directions. And I think that's accurate.

Dr. VON ESCHENBACH. Well, that's a very important point, Senator. And one of the other issues is, in the way in which this drug would be administered, it would not be available in convenience stores or supermarkets or places where people would have access without the opportunity to purchase it from a licensed pharmacist where that opportunity for guidance in how to properly use this can be provided by a professional.

Senator REED. But that would apply—I ask the question—that would apply to any age group, is that the——

Dr. VON ESCHENBACH. That's correct.

Senator REED. So, if a 30-year-old person walked in, and the pharmacist thought that they would have difficulties understanding the packaging, labeling, and the directions, he would, professionally, have the obligation to try to explain it, to ensure they knew that.

Dr. VON ESCHENBACH. The opportunity to do that. And I believe that would enhance public health.

Senator REED. And if a 17-year-old walked in, he would, similarly—or she would, similarly—have the professional obligation to do that.

It just seems to me that this line you're drawing is arbitrary, and it's being drawn for reasons unrelated to the actual dispensing of this medicine.

Dr. VON ESCHENBACH. Well, the application from the company created the bifurcation. The issue that I'm addressing is where that bifurcation should be. And 18 is a date, given all the commentary——

Senator REED. What was their original line of bifurcation?

Dr. VON ESCHENBACH. Sixteen.

Senator REED. Sixteen. And how did we go from—you, yourself, have said, "If you make it 18, we can talk."

Dr. VON ESCHENBACH. If we make it 18, we have extended that period of time in which young girls, who are in the midst of their reproductive development, where they—the data has not been adequate to assure that they will use this drug properly and appropriately as an emergency contraceptive, provides us, I think, a greater safeguard in protecting and promoting the health of these young girls. And I believe that, at the same time, we've provided a pathway where older women can have access to this drug in a way that could prevent unwanted pregnancies, that oftentimes, unfortunately, result in abortions. And I believe this, then, creates a dynamic in which we've protected and promoted public health.

Senator REED. Who first initiated, or suggested, a bifurcation? Was it the manufacturer or FDA?

Dr. VON ESCHENBACH. Well, as I understand the process, when the decision was made, based on the initial application, to not go forward because of these concerns, the company resubmitted an amended application with the bifurcation.

Senator REED. But their initial application had no bifurcation.

Dr. VON ESCHENBACH. Had no bifurcation. It was——

Senator REED. So, it was——

Dr. VON ESCHENBACH [continuing]. Without prescription for anyone and everyone.

Senator REED. But the FDA has gradually, or not so gradually, suggested that it be bifurcation. And I think the question, which I continue to pose is—I don't know, it doesn't seem to be a logical, appropriate break, based upon the behavior of people and the suitability that is variable at ages.

Dr. VON ESCHENBACH. Well, I think that—Senator, as you pointed out, the initial application was to make this available without prescription for anyone and everyone—12-, 13-, 14-year-olds, as well as older women—and the data did not support the safety——

Senator REED. A final question. And I think you've—in your discussions with Senator Murray, you've talked about this—but the data last year seemed, based on that letter, to be supportive of 17 and above. And she's asked, and I——

Dr. VON ESCHENBACH. Yeah.

Senator Reed. Is there new data? Is there new analysis? Or have you made a decision that you don't like the conclusion of your predecessor?

Dr. VON ESCHENBACH. The issue last year was, the company's application was 16. There was a question about the data not aligning with 16, and suggestion that it should be 17. In looking at the data, but also taking advantage of the benefit of what came out of the

discussion and the commentary for advance notice for proposed rulemaking, even though we're not going forward with that process, I believe that the more appropriate age bifurcation or cutoff would be 18.

Senator REED. Thank you.

The CHAIRMAN. Senator Clinton.

Senator CLINTON. Thank you, Mr. Chairman. And thanks, to our two witnesses, who are here.

I'd like to take a moment also to thank someone else, Dr. Susan Wood, who is here. I think Dr. Wood is here. If she would just, maybe, stand or raise her hand. Dr. Wood was the former director of the Women's Health Office at the FDA who resigned as a matter of principle over the failure to make a decision and the politicization of this process last year. And I think her principled stand is something that clearly speaks volumes about what we really believe is at work here, Dr. von Eschenbach.

And I want to make very clear, I agree 100 percent with Senator Hutchison's description of you, of your qualifications, of your experience. They are impeccable. You are caught, unfortunately, in a situation that gives great pause to many of us, because of what it means for the direction of the FDA. The FDA is, and should be, the gold standard for drug safety and efficacy. And, unfortunately, like so much else of this Government in the last 5½ years, it has been turned into a political football. And you're on the field.

So, we are directing these questions to you, because, unfortunately, given the way things run around here, there are very few opportunities for us to take stands on principle and to point out to the public what is at stake, because, unfortunately, this is not just about Plan B, although one would think, having listened to the previous Senators question you, that that's all you would do at the FDA. You know, the FDA is a very important agency for the sake of all of us, and I'm sure there are people in the audience, or maybe people watching on C-SPAN, who would say, "Well, that has nothing to do with me. I'm a 55-year-old man. I don't have any, you know, daughters. Why do I care about Plan B?"

I think the reason one should care is because once we start politicizing the FDA, there is no stopping. And, from my perspective, it is essential that we draw a line. And we're drawing the line right here. You know, somebody could come, in the future, and say, "They disapprove of smoking, so a new drug to treat lung cancer, directly related to smokers shouldn't be approved, because, by George, those people ought to just live with the consequences." Somebody could say, "You know, people need to start controlling their eating habits, so drugs and interventions, medical devices to deal with obesity, we shouldn't approve those. You know, it's immoral that people get obese, so let's make them have to learn the lesson." This is a slippery, dangerous slope we're on, Doctor, and we are looking to you to get a decision made.

And I have to ask you—you have great concern for the integrity of the FDA, and I applaud that—I want to ask you, under the circumstances of what many of us believe is at stake with respect to this decision, would you accept a recess appointment before a decision is made on Plan B?

Dr. VON ESCHENBACH. Senator, let me say, I want, and look forward to, the Senate's confirmation of me as your choice to be the Commissioner of the FDA. And I would hope that you would judge me on my record. I believe that I—the decision I made yesterday, and the principles upon which that decision was made, are exactly consistent with the principles that I alluded to with regard to the decision that was made about Tysabri, the decision that was made with regard to approving human papilloma virus vaccine, and all the other decisions. It has been based on my assessment of what the facts and the data and the science informed me, and informed the Agency, in my judgment. No one told me what I should, or could, do. No one told me what decision I must, or must not, make. This was my assessment and my commitment, and I hope you'll judge me on that record.

Senator CLINTON. Well, Doctor, last year, as my colleague Senator Murray pointed out, we were in the same position with the prior nominee to head the FDA. I want to thank the Chairman, who worked very closely with us to try to get some assurance that a decision would be made.

And I ask unanimous consent to put into the record a copy of the letter that Secretary Leavitt sent to Chairman Enzi.

The CHAIRMAN. Without objection.

[The information previously referred to follows:]

THE SECRETARY OF HEALTH AND HUMAN SERVICES,
WASHINGTON, DC 20201,
July 13, 2005.

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

DEAR CHAIRMAN ENZI: Per your request, this letter is to follow up on concerns that the Food and Drug Administration (FDA) has not acted on the application of Barr Laboratories to shift the product known as "Plan B" to over-the-counter for women 16 years of age and older, and prescription-only for younger age groups.

As you know, this decision rests solely with the FDA and must be made according to the scientific evidence and FDA's authority. Accordingly, I am not a part of this decisionmaking process.

However, I have spoken to the FDA, and, based on the feedback I have received, the FDA will act on this application by September 1, 2005.

I hope this is responsive to your request.

Sincerely,

MICHAEL O. LEAVITT.

Senator CLINTON. And, in the final paragraphs, he said,

> "As you know, this decision rests solely with the FDA and must be made according to the scientific evidence and FDA's authority. Accordingly, I am not a part of this decisionmaking process. However, I have spoken to the FDA, and, based on the feedback I have received, the FDA will act on this application by September 1, 2005."

And we know what happened. It did not. It, once again, failed to act, refused to act.

The GAO, in reviewing the history of this application, concluded it had been politicized, that people like Dr. Wood had every reason, on principle, to say this was not the FDA she had joined, this was

not the FDA that she had pledged her loyalty to, and so, she left, as so many others are now leaving.

In the letter that you sent, July 31, 2006, to Duramed Research—and, again, I ask unanimous consent it be admitted into the record.

The CHAIRMAN. Without objection.

[The information previously referred to follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
ROCKVILLE, MD 20857,
July 31, 2006.

NDA 21-045/S-001,
DURAMED RESEARCH, INC.,
Attention: JOSEPH A. CARRADO, M.SC., R.PH.,
Senior Director, Regulatory Affairs,
Bala Cynwyd, PA 19004.

DEAR MR. CARRADO: Please refer to your supplemental new drug application (sNDA) dated April 16, 2003, received April 22, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B® (levonorgestrel) Tablets, 0.75 mg.

In our August 26, 2005, letter to you we stated that the Agency was unable to reach a decision on the approvability of your application at that time because of unresolved difficult and novel issues raised by your sNDA. On the same day, the Agency issued an Advanced Notice of Proposed Rulemaking (ANPRM) seeking input from the public on certain issues regarding Rx to OTC switches, which related to the regulatory issues raised by your application. The comment period on the ANPRM closed on November 1, 2005, and the Agency received approximately 47,000 comments. FDA then hired a contractor to summarize and categorize the comments, and we received the contractor's final reports on May 19, 2006. FDA has reviewed the comments and, while they have provided the Agency with valuable insights regarding how the Agency might enforce an age-based restriction like the one proposed by your amended sNDA, we concur with the overwhelming majority of the comments (from individuals both for and against the approval of your sNDA) that it is not necessary to engage in rulemaking to resolve the novel regulatory issues raised by your application.

We are now proceeding with further evaluation of your sNDA. We would like to meet with you as soon as practicable, and preferably within 7 days, to discuss the status of your sNDA, including any necessary amendments. For example, your sNDA seeks approval for OTC use for women ages 16 and older. As we informed you in our August 26, 2005 letter, the Center for Drug Evaluation and Research concluded the available scientific data are insufficient to support the safe use of Plan B® as an OTC product for everyone in that age group. Moreover, because of enforcement considerations, we believe that the appropriate age for OTC access is 18. Should you desire to proceed with your sNDA, you would need to amend it to seek approval for OTC status for women ages 18 and older. An addition, you would need to amend your sNDA with respect to packaging.

We would also like to discuss the details of the CARESM Program that you submitted with your sNDA. That program regards your proposed marketing, education, distribution, and monitoring for the OTC version of Plan B®. Specifically, we would like to learn more about your proposal to restrict distribution of Plan B® to certain pharmacies, i.e., the OTC version of Plan B® would not be available at gas stations, convenience stores, etc., but only to those pharmacies agreeing to (1) keep the OTC version of the drug behind the pharmacy counter and (2) dispense the drug only upon the production of a valid photo identification card establishing the age of the consumer. In particular, we would like to learn more about your plan to routinely monitor these pharmacies to make sure they comply with the restricted distribution plan. In addition, we are very interested in learning how you plan on enforcing the restrictions if a pharmacy fails to comply with them, e.g., whether the restrictions will be incorporated into the terms of a formal contract and, if so, what the terms of that contract (particularly those terms related to a breach) look like. If after our discussions we conclude that the CARESM Program isn't sufficiently rigorous to prevent the OTC version of Plan B® from being used by young girls who can't safely

use the product without the supervision of a practitioner licensed by law to administer the drug, Plan B® will remain Rx-only for women of all ages.

Sincerely,

ANDREW VON ESCHENBACH, M.D.,
Acting Commissioner of Food and Drugs.

Senator CLINTON. You asked the company to explain how the company will enforce the restrictions if a pharmacy fails to comply with them. In other words, whether the restrictions will be incorporated into the terms of a formal contract. Is this unprecedented, Dr. von Eschenbach, that a company that submits an application to the FDA which is then going to rule on that as to whether or not it's available by prescription or over-the-counter, is going to be held responsible, in perpetuity, for what pharmacists and retail outlets do?

Dr. VON ESCHENBACH. Senator, there is precedent in a number of cases in which risk-management plans are a part of the application, and are——

Senator CLINTON. But the risk——

Dr. VON ESCHENBACH [continuing]. Considered a part of——

Senator CLINTON [continuing]. Management plans don't——

Dr. VON ESCHENBACH [continuing]. The approval.

Senator CLINTON [continuing]. Include having the company police it. They have warning labels, they have agreements with the pharmacy office. But you know, that would be as though—when we have law enforcement that goes and says to a liquor store or to a retail outlet that sells alcohol or cigarettes, and doesn't follow the law, that it's the maker of the product that is going to be held responsible. Is that what you're intending?

Dr. VON ESCHENBACH. What we're intending is to have a risk-management plan in place where there will be opportunities within that plan to be assured that, as this drug is being provided, it's being provided in accordance with the principles that we laid out in the plan. That is an issue that the company could oversee and take responsibility for. It could be a matter of sampling, from time to time, what happens when a young girl goes into a pharmacy to request this particular medication.

Senator CLINTON. Well, I would assume, then, that the requirements would be, in your words, "sufficiently rigorous," but not unprecedented, not beyond what has been expected of any other company. Is that correct?

Dr. VON ESCHENBACH. Yes. "Sufficiently rigorous" is, I think, an important way of describing that, but not that it is any way, shape, or form different than issues and ways that we would deal with any other drugs that require risk management.

Senator CLINTON. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you.

Senator Dodd.

Senator DODD. Thank you, Mr. Chairman.

Let me, first of all, thank both of our witnesses. I regret, in a way, we have both of you here simultaneously. I realize the constraints on the chair and the committee, but it's—I have a series of questions for both of you here, and, with the limited amount of time we get—both very important subject matters, obviously, as

you've heard. Most of the questions going to you, Doctor, but there are a lot of questions we have, Mr. DeCamp, for you. As the author of the Family and Medical Leave Act, I'm very interested, and I hope we'll have a chance, Mr. Chairman, to get back and come here.

But I want to followup on the issues that have been raised here with you, Doctor, and a number of other areas, and underscore the points that have been made by others already, raised by Senator Mikulski, and you've heard reiterated by my other colleagues, Senator Murray, Senator Reed, Senator Clinton, and that is the concern about the FDA. I've sat on this committee for a quarter of a century, and there's no other agency that has as much direct significance in the lives of the people we represent than the Food and Drug Administration.

Dr. VON ESCHENBACH. Yes, sir.

Senator DODD. And I think all of us who have been here over a number of years have taken great pride in the fact that—Republican and Democratic administrations, by and large—that Good Housekeeping seal of approval, FDA-approved, really, really has meant something. In fact, it's a standard, a gold standard, not just here, but around the world, in many, many ways. So, it is with a deep great of—a deep sense of concern that we raise these issues about what is apparently a rising level of concern within the scientific community about what's happening at FDA.

I was absolutely startled to read, here, that we talked about 420 FDA scientists reported—out of 997, when a survey was done—reported that they knew of cases in which the Department of Health and Human Services, or FDA, political appointees have inappropriately injected themselves into FDA determinations or actions—Vioxx, the SSRIs, Ketek. FDA has been accused of suppressing internal safety concerns, ignoring repeated warnings of safety concerns from FDA's own scientists.

In late 2004, FDA officials reportedly tried to prevent Dr. David Graham, from the Office of Drug Safety, from presenting his findings, demonstrating substantial cardiovascular risk from Vioxx. Dr. Graham claims he was told to change his findings and recommendations, because the FDA did not intend to make any additional labeling changes to the drug. Then-Acting Commissioner Dr. Lester Crawford did not intervene in this incident. The FDA denies suppressing the findings.

In 2003, another scientist in the Office of Drug Safety, Dr. Andrew Mosholder, reviewed data from more than 24 pediatric clinical trials for antidepressants. He found increased incidence of suicidal thoughts among children and adolescents taking the drug. FDA officials prevented the scientist from presenting his findings in the January 2004 Advisory Committee meeting on the drugs. It was not until the fall of 2004, more than a year after the initial study was completed, that the FDA issued a black-box label warning against pediatric use of most antidepressants.

And there's just case after case after case of these kinds of stories, and it's of great, great concern to us here. And, again, I underscore the points that have been made by those who presented you and introduced you. You've got an incredible record—a stunning record, really. I can't think of anyone who could bring a better set

of personal credentials and background to this job. We're just pleading with you here. I know the temptations in others. Don't go along with this stuff. We really are counting on you, if you're confirmed, to restore the confidence of this Agency. It is absolutely critical.

Now, I know that the Plan B issues are going to be raised again. I want to jump into a couple of quick areas, if I can. And Senator Clinton rightly points out, a lot of people out there are concerned about some other issues.

I've spent a lot of time on the pediatric drug issues. And I've written the legislation with Senator DeWine and others dealing with the Pharmaceuticals for Children Act and the Pediatric Research Equity Act. And I'm concerned about whether or not more authority is needed in some of these areas. I wonder if you would continue, first of all, to support the efforts to expand pediatric testing, which is something we care very deeply about; what steps the Agency could take to improve in this area; and to ensure that pediatric studies are answering the right questions and providing useful results. And is there any additional authority that you feel that Congress should provide to be helpful in this area? I wonder if, as well, would you take a look at whether or not we could be more effective, in terms of the delineation—differentiations on labels when a product is not approved for use in children because it has been shown, through studies, to be ineffective or unsafe, versus when it is not approved for children because it's just not been studied in that population.

I want to quickly jump, as well, to the issue of pediatric medical devices. Again, Senator Kennedy and others over the years have paid a lot of attention to these issues. The obvious problem here, with devices that were never suited to be used on infants and children, is the need to expand and to develop that area. And I'm very interested in whether or not the FDA would support or approve areas in which we could improve the production of medical devices for children. There's a 5- to 10-year lag behind those for adults in producing the technology that's necessary.

Let me ask you those questions first. And if you care to respond to my first point, the point that's been raised by others here, as well, I think you need a clearer statement on what you're going to do, if confirmed, on putting a stop to what clearly is a growing problem. When you listen to scientists who complain about the politicalization of your agency, or the agency you're heading right now, what are you really going to do? What message can you give us here today that would raise the level of confidence that the FDA is not going to be contaminated by this kind of thinking?

Dr. VON ESCHENBACH. Thank you, Senator.

And I am completely committed to the principle that you just espoused. The FDA has, and must continue to be, based on that sound scientific platform and infrastructure. And I will work to be sure that we continuously have processes, and continue to improve those processes—whether it's the appointment of advisory committees on the openness and transparency and those issues, and management conflict, whether it's providing opportunities with regard to creation of ombudsmen and pathways so that open scientific controversy can be discussed appropriately, or making certain that

when we come to closure and conclusion after all that process has been adequately exercised—that the public and those of you who hold the public trust can see and understand how those decisions were made and the basis upon which they were made. That is my commitment, and I will find every way possible to implement that.

As it relates to the very important area of pediatrics, I completely share with you the commitment that we need to continue to expand the opportunities to bring these lifesaving interventions into the pediatric population. We'll continue to work to find ways to enhance the ability to do the clinical trials and clinical studies that are necessary for the adaption of many of the things we're discovering in adults to be able to be applied to patients. I think continuing the opportunities to create devices that are, if you will, appropriate, miniaturized, if you will, for pediatric populations, ought to be given a very important priority. And I'll continue to seek mechanisms to enhance the ability to further the development of these interventions.

Senator DODD. Would you give a quick reaction here? Senator Grassley and I have introduced some legislation dealing with an independent office within the FDA on drug safety legislation. Senator Kennedy and the Chairman are also working on some legislation. We've had a number of incidences here, where the same department within the FDA that approves drugs, are also charged with the responsibility of going back and reviewing, after problems have arisen. Obviously, the inherent conflict of asking the same people who have approved a product being out in the marketplace, then asking the same people to make a judgment about whether or not there's a need for label changes or taking it off the market. It seems to me rather obvious, but I'd like you to comment on the wisdom of having some independent office within the FDA that could make those determinations, dealing with a variety of issues that have been raised with Vioxx and other such products.

Dr. VON ESCHENBACH. I would want to be sure that we had processes that were able to look at the issues of safety in an independent and appropriate way, but I would not want to separate, in a way, the issues that are related to understanding the efficacy or effectiveness of a drug and those issues that are associated with its safety, because as we move into the molecular era, and as we're seeing more and more of these opportunities that are coming from the Critical Path initiatives, for example, it is impossible, from a molecular perspective and a genetic perspective, to separate those. They are, in fact, part and parcel of each other. And so, I would like to see integration and coordination continue in a way that what we learn about the mechanism of a drug informs us as to whether it's going to be effective against a particular disease and whether it's going to be safe for that particular individual in that particular circumstance. And I think they're interwoven, and I want to keep that science and that knowledge base interwoven.

Senator DODD. Well, I understand that, but, just quickly, on the issue of the independence, once a product is out in the marketplace, and issues have been raised about it, as was with Vioxx and others, do you believe that the same office within the FDA ought to be making the determination as to whether or not some changes, ei-

ther in labeling or the usage, or even calling for that product to be withdrawn, should be done by the same office?

Dr. VON ESCHENBACH. I don't see, at this point, a need to change the mechanism that's currently in place, and separate those even more so, but to use the Office of Drug Safety and the consultation that's incorporated in that, that even comes from outside of the Agency, to really address that specifically and effectively.

Senator DODD. Mr. Chairman, I have——

The CHAIRMAN. The Senator's time has expired.

Senator DODD [continuing]. A load of other questions, and I'm going to ask unanimous consent that additional questions can be submitted to the nominee, if that's okay.

The CHAIRMAN. Absolutely.

In the initial remarks, I did say that we'd have a period of 10 days to get questions, and would ask for quick answers from both people. So, there will be that opportunity with both people. The record will remain open.

Senator CLINTON. So, Mr. Chairman, just to clarify, because I, unfortunately, am going to have to leave, also, we will be able to submit questions, and then we will be able to get answers to those questions, before any vote in the committee is scheduled?

The CHAIRMAN. Absolutely.

Senator CLINTON. Thank you.

The CHAIRMAN. Senator Harkin.

Senator HARKIN. Thank you, Mr. Chairman.

Well, Dr. von Eschenbach, I just want to take a couple of minutes on Plan B. I think Senator Clinton is exactly right, we all know what's going on here. It is a disregard of science for ideological concerns. How much have we seen that in this administration? Need I mention anything more than the stem cell debate and vote that was held here, in which science has been trumped by ideological concerns? That's what's going on here. And you know it as well as I do.

You know, here we are, in 2000, the American Medical Association said that this should be available over-the-counter without a prescription. In 2003, your Advisory Committee, 23 to 4, that it should be sold over-the-counter; 27 to nothing, they voted that the drug could be safely sold as an over-the-counter medication. Your own Advisory Committee, FDA. We know that.

Then I started—I asked about how many countries here. Forty-five countries now allow Plan B without a prescription—everything from Albania to Uruguay, Canada, Iceland, India, Israel, Morocco, Portugal, Sweden, Switzerland, Togo, Tunisia, United Kingdom, Uruguay—all these countries are permitting Plan B to be sold without a prescription to any young woman.

Now, you say you don't have enough data. You don't have enough data about young girls who are 13 or 14 or 12 or whatever. You don't have enough data. But it almost seems to me—and excuse me for saying this, because I have great respect for you—but, in saying that, you're saying that somehow our young women are stupider than the girls in these countries, that they're more illiterate, they can't even read a label. But the young women in Togo can, or in New Zealand, or Portugal, or Mauritania, or Mali, or Mauritius, or Benin. They can do it, but our young women can't.

How do you respond to that?

Dr. VON ESCHENBACH. Senator, I hope that you will accept the fact that I made this decision not on a political ideology, but on a medical ideology, that the data——

Senator HARKIN. Medical?

Dr. VON ESCHENBACH [continuing]. That you're alluding is not there to suggest that 12-, 13-year-old girls can understand how to use this drug without medical supervision. And without that data being present, my ideology, and what I hope to always express, as the Commissioner of the FDA, is to protect and promote their health and welfare. And the decision was based on the fact that they should not have access to this drug without medical supervision. That's the ideology that is——

Senator HARKIN. Are you saying this of yourself? They should not have it without medical supervision. Is that what you're saying——

Dr. VON ESCHENBACH. I——

Senator HARKIN [continuing]. Of yourself?

Dr. VON ESCHENBACH. I believe that the application, as it had been reviewed, the decisions that were made by the Center director affirmed and supported that position, and I also affirm and support that decision. So, that as we're going to have to go forward with this application, as I'm prepared to do, it has to have a risk-management plan. And it is common with other risk-management plans to ask the company to be part of that agreement and to help police enforcement, so we're not doing anything different.

Senator HARKIN. Well, Dr. von Eschenbach, with all due respect, I think you're going way far afield here on this one. I think you're going way far afield on this. I don't know all the data, myself, but I just think the FDA is getting into an area that's not as from—and I've been on this committee a long time—in an area that I've not seen it tread before.

Dr. VON ESCHENBACH. Well, I appreciate that, Senator, and I think this particular application, with this high-dose hormone being available to young girls——

Senator HARKIN. But all of these——

Dr. VON ESCHENBACH [continuing]. Is a unique circumstance.

Senator HARKIN. Forty-five other countries—United Kingdom, Canada, our neighbor to the north? Give me a break. Australia? I'm just talking about, sort of, the English-speaking countries. Now we can go to—we can go now to Islamic countries, we can go to India, Israel——

Dr. VON ESCHENBACH. Well——

Senator HARKIN [continuing]. Iceland. I mean, give me a break.

Dr. VON ESCHENBACH. Can I point out, in many of those cases that you just alluded to, Senator, I think that what they are, in fact, doing is providing it, as we would describe it, as behind-the-counter. It is being provided, but it's being provided in the context of it being behind-the-counter, which is in line with——

Senator HARKIN. I don't know' em all, but I know, in France, it's done with school nurses. A young girl can go——

Dr. VON ESCHENBACH [continuing]. With——

Senator HARKIN [continuing]. To the school nurse and get it.

Dr. VON ESCHENBACH. With medical supervision, yeah.

Senator HARKIN. That's fine. Would you be in favor of that here? School nurses? I don't know. I shouldn't—you probably shouldn't answer——

Dr. VON ESCHENBACH. It——

Senator HARKIN. You probably shouldn't answer that question.

[Laughter.]

Senator HARKIN. I don't want to get into that.

Can I move to something——

Dr. VON ESCHENBACH. Sure.

Senator HARKIN. I just think this Plan B is going to be real trouble. It has to—and this, kind of, leads into my next question, in terms of scientific integrity at FDA.

The Union of Concerned Scientists recently sent a survey to 5,918 scientists at FDA. A thousand responded. The survey asked a series of questions about political interference with scientific findings. Here are some troubling findings in the survey: 20 percent said they "have been asked explicitly by FDA decisionmakers to provide incomplete, inaccurate, or misleading information to the public, regulated industry, media, or elected officials." In addition, 40 percent said they could not publicly express, "concerns about public health without fear of retaliation."

As a scientist, do you believe there is ever any reason for political appointees to change, edit, emphasize, de-emphasize, or otherwise alter scientific findings? Want me to repeat that? As a scientist——

Dr. VON ESCHENBACH. Yes.

Senator HARKIN [continuing]. Do you believe there is ever any reason for a political appointee to change or edit, de-emphasize, emphasize, or otherwise alter scientific findings?

Dr. VON ESCHENBACH. No one should ever alter scientific findings.

Senator HARKIN. As the head of the National Cancer Institute, did you ever ask any scientist under your jurisdiction to edit, change, emphasize, or de-emphasize, or otherwise alter any scientific findings?

Dr. VON ESCHENBACH. Not the scientific data or the findings, no, sir.

Senator HARKIN. OK. And how will you ensure that politics does not substitute for sound science? I just read you the survey that was taken. I mean, this is going on right now at FDA.

Dr. VON ESCHENBACH. There is a very important set of issues that you are addressing and alluding to that I intend to be personally responsible for and address. I think the survey—and there are other surveys that I have looked at—indicate the fact that we are in the process of being able to continue to improve our mechanisms and our processes with regard to openness and transparency. We've created guidances very recently with regard to our ability to manage our advisory committees. And this is a continuous quality improvement.

There is another issue, Senator, on the other side of it, and that is, when we talk about scientific deliberation and discussion and debate, no one should ever alter the data or the scientific facts, but there are differences of opinion that arise with regard to the interpretation——

Senator HARKIN. Interpreting. I understand that.

Dr. VON ESCHENBACH [continuing]. Of those facts.

Senator HARKIN. Sure.

Dr. VON ESCHENBACH. And that is an area in which, once consensus is arrived, if they don't happen to be one individual's point of view, that does not necessarily mean that that individual was right and the consensus was wrong. And because they protest or assume that somehow or other their point of view wasn't the accepted one, doesn't mean theirs was the right one.

Senator HARKIN. You're right. Scientific certainty is not an absolute.

Dr. VON ESCHENBACH. The data informs the decisions, but the decisions are made with judgment.

Senator HARKIN. I'm running out of time. I just want to ask him about salt. And you're thinking, "Boy, this guy's going far afield."

The FDA still regulates as GRAS, generally recognized as safe, salt.

Dr. VON ESCHENBACH. Uh-huh.

Senator HARKIN. The Dietary Guidelines for Americans urging them to reduce their intake of salt. Everyone says high blood pressure, Americans have got to reduce their intake of salt. However, FDA's continued treatment of salt is not consistent with HHS and USDA recommendations. Do you anticipate in any way revisiting the issue of the GRAS, the generally recognized as safe, status of salt, or taking any additional steps to decrease salt consumption in America?

Dr. VON ESCHENBACH. Yes, Senator, we are. And the Agency is intending to really solicit much more information with regard to even holding a future public hearing. We do collaborate and cooperate with the other components of the Department, in terms of establishing a healthy diet for Americans. And so, we'll continue to stay engaged and committed to addressing this question.

Senator HARKIN. Last, Mr. Chairman—please go after this: Liquid Zoo. These are the flavored cigarettes that are going out to kids. FDA has got to get stronger on this. You've got to start regulating Liquid Zoo, strawberry-flavored cigarettes that hook kids onto smoking right now. And, again, we've passed legislation before. There's overwhelming support. And FDA ought to have regulatory authority over stuff like this.

Dr. VON ESCHENBACH. Thank you, Senator.

Senator HARKIN. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you.

Mr. DeCamp, I don't want you to feel neglected.

[Laughter.]

You've moved from a private practice to being a government advisory. Now you will be moving from being an advisor to being an administrator. The committee is aware of your significant career in employment law. You've represented many clients in employment-related litigation, and written a number of articles on Fair Labor Standards Act. Through these experiences, have you formed a philosophy on the appropriate approach for this enforcement agency? What do you believe the Wage and Hours Division's priority should be? What could the Agency do to better protect American workers?

Mr. DECAMP. Ultimately, I think the most important thing that Wage and Hour does is to protect workers. There are obviously a lot of statutes that the Agency is responsible for administering, and it is the job of the administrator and the Agency to enforce those statutes correctly under the law, but vigorously and fairly and completely. And I think that that is the most important thing that the Agency does.

In terms of being more specific about that, one of the things that the Agency needs to do, and an activity that I would focus on, is increasing our responsiveness to complaints that come in. The Agency has worked hard over the past several years to decrease the amount of time that it takes, for example, from when a complaint is received by an aggrieved worker to actually getting that complaint resolved. And so, continuing along that road, and trying to be better service oriented to the people who are bringing complaints, that's the first area.

The second area would be to continue the Agency's targeted enforcement activities with regard to low-wage workers, workers who are economically vulnerable, workers who, for various reasons, perhaps because of immigration status or other concerns, are perhaps under-reporting claims and are more likely to have their rights violated, without aggressive enforcement on the part of the Agency. So, helping those who are less likely to be able to help themselves.

Third, working on updating the child labor regulations, which have not been significantly revised in about 30 years. I think it's essential; in part, because there is no private enforcement, no private-sector enforcement of the child labor regulations. The Department of Labor is, in effect, the only show in town on that issue. And so, the Department needs to, in my view, really focus on making sure that the regulations continue to reflect what is known about the risks to youth and employment, and to protect the youth, based on current information, including a report that was submitted by NIOSH in 2002.

The CHAIRMAN. Good. Changing subjects pretty drastically here, Senator Kennedy and I, and others, traveled to New Orleans and the Gulf Coast immediately following Hurricane Katrina, and we saw the catastrophic damage that occurred. Work is being done in that area that requires a lot of labor resources, time to rebuild and a lot of hard work, but there have been reports of labor abuses, such as the failure to pay overtime. And there are allegations that the Department of Labor is not doing enough to enforce the laws in the region.

I know that the Wage and Hour Division has sent a task force to the region to investigate the allegations of noncompliance. As head of the Wage and Hour Division, can you tell me what kind of priority you'd place on that work?

Mr. DECAMP. If confirmed, I would definitely want to emphasize that work. This is a region, in the Gulf Coast, where the infrastructure was largely decimated, where even our own workers, even the Agency's own workers, were personally affected by the hurricane. For example, one of our district directors had no hot water in her own home for approximately 6 months following the hurricane. So, it was very disrupting to the lives of the Agency's workers, let alone the many other workers who were in that region.

One of the steps that the Agency has taken is—in addition to trying to get our own workers back up and running and on their feet in the region—we've been bringing in workers on detail, bringing in investigators on detail, from other parts of the country to supplement the workers who are already there on the ground in the Gulf Coast.

In addition, as part of the 2007 budget request, the Agency, the Department, has sought additional funding for additional investigators; specifically, has sought an addition of $6 million for an additional 39 investigators, which, if granted—if that money is appropriated, certainly some portion of that would, perhaps, be available for assignment either on detail or permanent assignment into the Gulf Coast region.

The CHAIRMAN. Before my time runs out, I also have to bring up a pet project that I've been working on. Most of Wyoming's firefighting is done by volunteers. And you may not be aware that approximately 75 percent of all firefighting service in the United States is provided by volunteers. For some time now, the International Association of Fire Chiefs representing these volunteers has been seeking clarity from the Department of Labor's Wage and Hour Division about their status under the Fair Labor Standards Act. They need to know when a nominal fee rises to the level that would classify a volunteer as an employee. The request for guidance was made in July 2003, and they're still waiting for an answer, despite a number of meetings and my own request that the Department respond. As head of the Wage and Hour Division, would you work to promptly respond to this request for clarity? Do you think that 3 years is a reasonable amount of time to wait?

Mr. DECAMP. If confirmed, I would certainly work to get that issue resolved as expeditiously as possible. I'm familiar with the issue. It's a question of section 3(e)(4)(A) under the Fair Labor Standards Act. It's an important issue. It's one that arises in a variety of contexts. And, if confirmed, I would work to get resolution on that issue promptly.

The CHAIRMAN. Thank you. I appreciate the brevity of your answers, too.

Senator Kennedy.

Senator KENNEDY. Thank you, Mr. Chairman.

I ask consent that the testimony of Mr. Samuel, legislative director, AFL-CIO, be included in the record.

The CHAIRMAN. Without objection.

[Editors Note: The information previously referred to was not available at time of print.]

Senator KENNEDY. And, as I understand, other members will be able to ask questions of the panel, and in a timely way.

The CHAIRMAN. Absolutely. Yes, we'll leave the record open, so——

Senator KENNEDY. We'll have a short period of time, Mr. DeCamp. I'd like to keep—there's a lot of areas I'd like to cover. One is this—today marks the 10th anniversary of the last time this Congress voted for an increase in the minimum wage. We have a proposal that's coming over from the House of Representatives attached to the estate tax. Do you have a view about the increase in the minimum wage? Do you support that proposal? What is——

Mr. DECAMP. My view is that, if confirmed, the most important thing that an administrator can do is to enforce the law, as written. And I certainly appreciate and understand the importance of minimum wage, in particular, to employees who are economically vulnerable.

Senator KENNEDY. But you don't have a position on the increase in the minimum wage.

Mr. DECAMP. With respect, Senator, I've been——

Senator KENNEDY. OK.

Mr. DECAMP [continuing]. Nominated for an enforcement position, and not for an economic——

Senator KENNEDY. Well, there's——

Mr. DECAMP [continuing]. Policy position.

Senator KENNEDY. Those are going to be—that's, under the Fair Labor Standards Act, enforcement of it. So, they also will be decreasing the number of businesses subject to the requirement, and then pre-empting the States on the Federal standard on the tipped employee. So, it's, sort of, one step forward and two steps back.

I noted in your response that you gave us, in answering questions, on April 24, you talked about the fact that now you're working with the Secretary and other senior Department officials, and one of the areas you're going in is the Gulf Coast region, also day laborers, also independent contractors. The GAO has just issued, and were releasing today, a report about independent contractors, and it is critical of the Department of Labor. You've had some responsibility over there. Why should we think you're going to do a better job in defining the rights and the protections of workers, when the GAO finds that the Labor Department has failed, in terms of getting information out and defining the definition of who is an independent contractor and who isn't, and who, therefore, will get protection for the range of different protections of the Fair Labor Standards Act?

Mr. DECAMP. Senator, I've not seen the report, obviously, but what I would note is that the issue of independent contractor versus employee is a very difficult, challenging question under Federal law. It's one of the tougher questions under employment law. There is no easy, bright-line test for it, and it involves a multitude of factors. I can say, from personal experience, I have been classified as an independent contractor in the past, and I know that—the burdens that go along with that, including having to pay double taxes and not getting overtime and not getting any regulation of hours. My involvement in—with regard to independent contractors at the Department, so far—was really tied to the notion of day laborers and the Gulf Coast, and finding ways——

Senator KENNEDY. OK.

Mr. DECAMP [continuing]. To try to protect——

Senator KENNEDY. All right. Well, let's get to those, although I'll refer you to the GAO, particularly on pages 31 and 32. Let's get to Gulf Coast. You mentioned—this is the report by the National Immigration Law Center. The Chairman mentioned—very quickly, we're all caught on the time, but this is an extensive report about the absolute disastrous circumstances for workers, and worker protections, down there. It talks about a whole range—personnel wage theft, rampant wage theft, many different types of wage theft—

page after page after page. This was an area that you say you had some responsibility of. This is about a fierce indictment, in terms of what is happening down—even with all the complex circumstances down there. It's illustration after illustration after illustration, story after story after story. And they said that the Labor Department was missing in action, as AWOL. This was an area of responsibility that you had, that you just admit to it now, you say, in here—why are we going to think that these workers are going to get protected?—and you say, "Well, we get the 39 detailees." Detailees, as you well know, only work 2 weeks in a particular assignment, they don't stay—they don't go on down there and stay. It's 2 weeks. That's what they—it is in the Department of Labor. Why should we think that you're going to do a better job?

Mr. DECAMP. With regard to detailees, it's not just sending somebody down for 2 weeks and then they're gone. It would be rotating detailees in——

Senator KENNEDY. All right.

Mr. DECAMP [continuing]. To try to increase the——

Senator KENNEDY. But your reaction to this report, you said, in your statement, "with Gulf Coast region" and you also indicate independent contractors—we have a GAO report that says the Labor Department has failed, in terms of meeting its responsibility of contractors. You indicated the Gulf region. We have the report here that is a fierce indictment of the Department of Labor by the National Immigration Law Center, chapter and verse, on this issue. And, on the day laborers, what have you done in terms of bringing cases against employers that are exploiting undocumented workers? How many suits has the Labor Department brought against employers for undocumented workers in this last year since you've been in?

Mr. DECAMP. I don't know about the number of lawsuits with regard to undocumented workers.

Senator KENNEDY. You know how—what has been recovered or what the penalties have been? Does——

Mr. DECAMP. In the——

Senator KENNEDY [continuing]. Three sound about right?

Mr. DECAMP. In the Gulf Coast, there have been approximately 300 hurricane-related cases that the Department has been investigating, including bringing over a hundred of them to conclusion and recovering in excess of $1.3 million in back wages. There are, in addition, about 200 cases or so that are still in process. The Department has pursued remedies under the Service Contract Act, including withholding, including debarment. And those statutes—they do confer certain procedural rights on employers, and so, those cases are working their way through the system, but the Department is pursuing those. And, if confirmed, I would vigorously enforce those statutes and try to assign additional resources to the region to make sure that the workers are being protected.

Senator KENNEDY. Well, my time—and on the day laborers, these are individuals, more often than not, undocumented. We've got a big issue on the immigration. But one of them is effective enforcement. And this is an area where the Department—we hear much from a lot of our speakers around here, "We've got to have law enforcement." And here, we have the Labor Department's—I believe

it's been three cases, penalties somewhere around $300,000, nationwide. Does all of that ring a bell or——

Mr. DECAMP. I'm familiar with the Department's efforts to try to protect day laborers, but those issues are very complex, and one of the hardest parts about the issue is to reach the day laborers to make sure that they understand their rights. They're, in many instances, because of their immigration status, reluctant to approach the Department, for fear of deportment of other kinds of adverse consequences from law enforcement. And so, part of the issue—and this has played out in the Gulf Coast, as well—is trying to gain the trust of these workers so that they will come to the Department or work through intermediaries, such as community groups and advocacy groups, to let us know where the rights are being violated so that we can protect them. That's an area where continued work is necessary.

Senator KENNEDY. Let me just, finally—and I thank the chair—how many contractors have you sought to debar under the Davis-Bacon and Service Contract Acts?

Mr. DECAMP. My understanding is that several are in process, where the remedy is being considered. And I believe it's at least two or three. If confirmed, I would be——

Senator KENNEDY. Two or three?

Mr. DECAMP. That's my understanding. There may be more. If confirmed, I would certainly make sure that the field personnel understand that they should use that, and any other available remedies, including withholding and other appropriate remedies, to make sure that their rights are being enforced vigorously.

Senator KENNEDY. Thank you, Mr. DeCamp, thank you. I apologize for interrupting you. And there's a whole series of areas in here. I'll submit these additional questions in writing, and some followup questions. I appreciate—thank the chair.

The CHAIRMAN. Certainly.

Senator Murray.

Senator MURRAY. Thank you, Mr. Chairman. And I just have one more line of questioning for Dr. von Eschenbach. I hope to have time to ask Mr. DeCamp a question, as well.

The only other case I know of, where FDA puts the burden on the manufacturer, is Accutane. Because it can cause serious birth defects. Unlike Plan B, which has no side effects, Accutane has very serious side effects. And we know that the requirements for women taking Accutane is, they have to be on two contraceptives. Do you have any concerns about girls who are 17 or 18 being able to understand the instructions with Accutane, which is to be on two forms of contraceptives while taking it?

Dr. VON ESCHENBACH. It's my understanding, Senator, that within that risk-management plan for Accutane it is intended to be able to guide and direct them to the appropriate and proper use of Accutane.

Senator MURRAY. So, you understand that those women can understand the directions that go with taking it, because it has very serious side effects. So, I don't understand why you're concerned about women who are 17 or 18 being able to understand instructions for Plan B——

Dr. VON ESCHENBACH. Well, the 18-year-old——

Senator MURRAY [continuing]. Which has no side effects.

Dr. VON ESCHENBACH [continuing]. The 18-year-old bifurcation was derived from the comments that came out of the process for advance notice for proposed rulemaking with regard to guiding enforceability of a bifurcation in the application. And, at the same time, it——

Senator MURRAY. Are you talking about Plan B?

Dr. VON ESCHENBACH. Right. So, the concern I have with regard to the 18-year-old bifurcation——

Senator MURRAY. Came from the questions, so the public opinion influenced you on that?

Dr. VON ESCHENBACH. The indication of how we could, in fact, provide enforceability of it being both prescription and nonprescription at the same time. And the issue with regard to its safety is around the issue of misuse or inappropriate use in the context of the——

Senator MURRAY. But you don't have concerns about Accutane, which has serious side effects——

Dr. VON ESCHENBACH. Well——

Senator MURRAY [continuing]. For a woman to be able to understand those instructions?

Dr. VON ESCHENBACH. I agree with you, Senator. I do have concerns about Accutane, as well. And there is a risk-management plan in place that was, in fact, intended to address those concerns, as well.

Senator MURRAY. Well, I think it leads us all to the question of how the decisions are made. We've been down this road, and I will let it go, at this point. But, to me, it seems very important, Mr. Chairman, that we have a decision on Plan B, so we can put all of these questions behind us and have someone at the head of FDA that we all can count on.

But I do want to ask Mr. DeCamp a question. And I listened to your opening remarks, and you talked about your career and all the washing dishes and mopping floors, which I assume was in high school, since you didn't include those in your qualifications statement to the committee.

Mr. DECAMP. High school and college.

Senator MURRAY. High school and college. Well, given your working-class background, I was surprised, then, that your professional career has really been defending employers against workers in a wide range of employment matters. And, in particular, you chose to work for Wal-Mart in appealing the certification of a nationwide class of 1.6 million women who were alleging systematic gender discrimination in pay and promotions. So, listening to you talk about your working-class background, I was surprised, and would like to hear from you why you chose to defend a company with a history of questionable employment practices against a group of—very large—low-wage women, and their pay.

Mr. DECAMP. The focus of my career, in law practice, was on the law. It was on protecting the rights of clients of the law firms where I worked. And it has never been anti-worker, it's never been pro-employer. It's been defending clients. Specifically, one of the insights that I've had from working with employers——

Senator MURRAY. Do you think that the 1.6 million had a case?

Mr. DECAMP. My firm's involvement in that case had nothing to do with whether, individually, they had been the victims of sex discrimination in pay and promotions, which was the underlying claim; my firm's involvement was limited to the question of whether the procedural remedy of class certification was appropriate in that instance. In my view and the view of the client at the time, the view was that the District Court had erred, had incorrectly construed the law——

Senator MURRAY. Do you think there's ever a case where women have been discriminated on by gender?

Mr. DECAMP. Oh, absolutely. Of course. And——

Senator MURRAY. Can you tell me when that was?

Mr. DECAMP. There have been lots of meritorious claims where women have prevailed in claims against all kinds of employers for sex discrimination. I have no——

Senator MURRAY. That you think were legitimate?

Mr. DECAMP. Absolutely. Absolutely. The issue in the Dukes case was the procedural class certification that of whether the case should—in other words, proceed as a nationwide class action of 1.6 million people, versus store-by-store class actions or some other smaller aggregation. There were evidentiary problems in the case that made a nationwide class action improper, but that says nothing about whether individually or in smaller groups the women had perfectly——

Senator MURRAY. So, you think it would have been better for the women, one by one, to come forward and go after Wal-Mart.

Mr. DECAMP. One by one, or on a store-by-store basis, which would be——

Senator MURRAY. You think that's fair?

Mr. DECAMP. I think it's——

Senator MURRAY. Wal-Mart against one woman, who gets minimum wage?

Mr. DECAMP. It's not—under the law, class certification has certain requirements. And, in our view, the law of class certification was not satisfied with regard to what the District Court did in that case. It is entirely possible—and in the briefs, the client argued—that smaller class actions could well have been appropriate in that case, but not a case that, in essence, tries to take stores where there were statistics indicating gender disparities, and lump them in with stores where they were indicating—where the evidence showed that there were no disparities. The problem was that you had a——

Senator MURRAY. Well, have you ever defended a worker in a lawsuit against an employer?

Mr. DECAMP. I have not. My firm represented employers with regard to employment disputes. That's the nature of private bar. It tends to be that law firms will represent either employees or employers, but not both, because of the issue conflicts that are presented. One of the insights that I got from working in private practice was that whether you're talking about employers or employees, you're talking about people, and most of them, whether it's employers or employees, are good, and tend to do the right thing; some do not, some get it wrong, whether it's employees or employers. If confirmed, I would very vigorously go after employers and enforce

the laws with regard to employers who have broken the law. I believe, absolutely, that—whether it's Wal-Mart or any other business in the country—that they have to follow the law, they have to respect the rights of workers that are set forth in Federal statutes. And I take that obligation absolutely seriously.

Senator MURRAY. Well, I see my time is out, Mr. Chairman. I do have a number of questions for both of the nominees, and my understanding is that we have 10 days to submit the questions. How long will they have to respond to them?

The CHAIRMAN. I'm hoping that they will respond rapidly so that we can continue on with the process. We'll be gone during August.

Senator MURRAY. Right. So, I assume it'll be September before we have a chance, in this committee, to—if you are going to bring it up for a vote.

And my question is—because there's a lot of rumor about a recess appointment for the FDA Director. And since we have time to submit questions, they will have time to respond, I assume that there won't be a recess appointment while we are still having the opportunity to look at the questions and responses.

The CHAIRMAN. That's not a decision that I can make, nor is it one that anybody's talked to me about.

Senator MURRAY. Thank you, Mr. Chairman.

The CHAIRMAN. I want to thank Dr. von Eschenbach and Mr. DeCamp for their testimony, their responsiveness, their vast range of knowledge, and, probably most of all, their willingness to serve, realizing that they would have to go through a hearing like this.

[Laughter.]

I also want to thank my colleagues for their interest and attendance, and the way that they've addressed questions, and their thoroughness. I do look forward to working with both of you, and to working with my colleagues to move these nominations to the Senate floor.

Both rounds of questions have been completed. I will reiterate, again, that the members of this committee will be submitting additional questions in writing to both of you. I would note to my colleagues that if they intend to propound any written questions, that these questions have to be submitted within 10 days following the adjournment of today's hearing, and we would ask that the nominees provide their responses as quickly as possible so there would be no inordinate delay in completing the confirmation process.

Again, thank you very much for your participation today.

We had said that we would go into an executive session. We do not have a quorum for an executive session, so the executive session is postponed, and that date and time will be announced shortly, and will probably be with a vote tomorrow.

So, at this point, the hearing is adjourned.

ADDITIONAL MATERIAL

RESPONSE TO QUESTIONS OF SENATOR ENZI BY ANDREW C. VON ESCHENBACH

Question 1. Our regulatory system is data and science driven. In the past, the FDA has not accepted post-hoc subgroup analysis without further data collection on the subgroups. For example, in withdrawing the lung cancer drug Iressa from the market, the Agency pointed out that suggestions of efficacy in a subgroup were not enough. In considering action on the Plan B emergency contraceptive, what data did you use to pick 18 as the age cutoff for nonprescription access? The 2004 Plan B application used 16 as an age cutoff, while the label comprehension study used 17 as a breakpoint in age groups. If the switch to 18 was not data-driven, what authority was the decision to use 18 based upon?

Answer 1. The Center for Drug Evaluation and Research (CDER) at FDA determined that the data submitted by the sponsor (Duramed or Barr) in its 2004 application supported OTC use for women 17 and older. In considering the difficulty of enforcing an age-based restriction on the availability of this oral hormonal contraceptive, however, I have concluded that 18 (rather than 17) is the more appropriate cutoff to best promote and protect the public health. The State-regulated pharmacies that will be dispensing Plan B® under Barr's voluntary Convenient Access, Responsible Education (CARE) program (as well as society as a whole) are more familiar with 18 as a cutoff age. I understand that in all 50 States, 18 is the age of majority (i.e., the legal delineation between minor and adult), and retail outlets, including pharmacies, are familiar with using 18 as the age of restriction for the sale of certain products. With regard to drug products, for example, the legal age to purchase FDA approved non-prescription nicotine replacement therapy products is 18. Moreover, I understand that as a matter of State law, many products routinely sold by pharmacies, e.g., tobacco products and nonprescription cough-cold products like pseudoephedrine are restricted to consumers 18 and older. The approach builds on well-established State and private sector infrastructures to restrict certain products to consumers 18 and older. This approach should, therefore, help ensure safe and effective use of Plan B.

Question 2. Restrictions on distribution and use, although somewhat rare, are not unheard of for prescription drugs. Are there nonprescription drugs that have restrictions on distribution or use? In the case of prescription drugs with restrictions on distribution and use, who is responsible for enforcing those restrictions? What role does the manufacturer of the product typically play in enforcing those restrictions?

Answer 2. The FDA-approved labeling for nonprescription nicotine replacement therapy products states that they are for use by consumers 18 years of age and older. In addition, some States have restricted nonprescription cough-cold medications like pseudoephedrine to consumers 18 and older. In this case, the company proposed to market prescription Plan B and nonprescription Plan B in the same box. Therefore, certain marketing restrictions are appropriate to ensure that Plan B is made available to one population on a prescription basis and another population on a nonprescription basis. Both FDA and manufacturers are involved in ensuring that restrictions on distribution and use are followed. Manufacturers typically submit, as part of their application, a plan to address any marketing restrictions, which often includes, as here, education and monitoring.

Question 3. The Critical Path Initiative is an important collaboration between the Agency, industry and academia to develop new tools to evaluate medical products. The Opportunities List was released in March of this year, identifying 76 project areas for research. How many of these projects are moving forward? Have you seen the sort of response you had hoped to these proposals? When do you expect to see some results from these projects?

Answer 3. Within current resources we have been able to initiate projects in all six priority areas discussed in the Opportunities Report and List. For example, we have been able to initiate several collaborations described in Opportunity #2, to ensure that micro-array technology can be used for biomarker identification in product development. A collaboration involving the NIH and others to validate FDG-PET as a response measure in nonHodgkins lymphoma is already writing the clinical protocol (see Opportunity #26). We are actively working on concept papers toward developing consensus on more innovative clinical trial designs (see Opportunity #34–37). In the next few weeks, we will publish a followup report describing specific Critical Path projects we are undertaking in calendar year 2006. (Timeframe for results varies across the projects, and often depends on the resource commitment not only of FDA but of our collaborating partners.)

Based on the many inquiries we have received regarding potential partnerships with FDA on Critical Path projects, we believe the Initiative is already having an effect on how industry, academia, and others think about product development sciences. We hope stakeholders will use the List and Report to begin planning their activities in the national effort to modernize the Critical Path sciences. Since the List and Report have been out for only a few months, and the timeframe for planning research and development activities is longer, it is too soon to assess whether this is occurring on a broad scale.

Question 4. Some of my colleagues have proposed a separate drug safety office on the theory that scientists who make a decision supporting marketing of a drug would be reluctant to change that decision in light of new data. FDA scientists have integrity, talent and dedication, and I find it hard to believe they would or even could ignore what the data is telling them. Isn't science an inherently self-correcting enterprise? Please comment on how the drug review and post-market evaluation processes incorporate science into decisionmaking.

Answer 4. The decisionmaking processes at FDA incorporates science at all levels. FDA medical reviewers and scientists make regulatory judgments based on scientific data during both the drug review and post-market evaluation processes. The Agency makes these decisions in an open, transparent, and collaborative environment that offers several mechanisms for resolving differing scientific opinions. We weigh the scientific data regarding the inherent benefits of a product against its risks, and based upon the judgment of our medical reviewers, experts, and management about what that data tell us, we ultimately make a regulatory decision about that product. Over time, as the science underpinning our decisions changes and as we get new information regarding the basis and standards for our decisions, we move to re-visit our processes and respond to the new scientific information as appropriate and as necessary.

With respect to a separate drug safety office, the nature of our knowledge of a drug's safety profile and the expertise required for the ongoing assessment of a drug's risk-benefit balance demand that these two activities be housed in a single center. Our knowledge of a drug's safety profile proceeds along a continuum, which begins with *in vitro* and animal studies (before the drug is ever administered to humans), continues to grow through rigorous clinical trials, and is further refined after a drug is marketed. It is the review and synthesis of this cumulative knowledge base that leads to the most accurate assessment of the drug's safety profile. In CDER, Office of New Drug (OND) staff is the most knowledgeable about the premarketing safety data, while Office of Surveillance and Epidemiology (OSE) staff specializes in the post-marketing safety issues. Staff from the OSE and OND work closely in the analysis of appropriate regulatory actions, together they take into consideration both risk and benefit information from pre- and post-approval sources. If pre-approval and post-approval functions were split, there would be a loss of continuity in the review of risks and benefits.

Additionally, separating these two activities into two centers would be very costly, because of the duplication of the wide range of expertise involved. Medical officers in OND whose areas of expertise include the affected patient population(s), medical conditions, and treatments, know the results of animal and clinical studies that supported approval of the product; in addition, they review studies with products that are used in the same patient populations, and products, some still in the investigational phase, from drugs in the same or related classes. This expert knowledge of the patients' medical conditions, availability of alternative therapies, and safety profiles from IND and NDA submissions is a crucial component in the review of newly identified risks and how they may impact benefits. OSE personnel provide expertise in the areas of epidemiological studies of large populations, evaluation of data from AERS (that is, spontaneous adverse event reporting) and large external data sets purchased for adverse event tracking and evaluation in specific populations, medication error prevention, and risk management techniques.

If the responsibilities were split into two centers, the safety center would have to duplicate the expertise of OND staff, with expert knowledge of patient populations, medical conditions, alternative therapies, and safety profiles from investigational new drug applications and studies in marketing applications to support approval to enable the safety center to make appropriate risk-benefit decisions and the drug approval center would have to duplicate the expertise of the OSE staff. Cross-center consultation would be much more difficult, and therefore, less efficient, than within center collaboration.

OND routinely meets with OSE staff to discuss the current or anticipated safety of marketed products. In addition, CDER has recently instituted safety meetings that are held periodically (monthly or bi-monthly) to discuss new safety issues and

the status of reviews and analysis of previously identified safety signals. Also, prior to approval of applications to market new molecular entities (NMEs), or nonNMEs, OND and OSE staff have pre-approval safety conferences. The OSE staff is also consulted by OND in many pre-approval activities that increase CDER's ability to understand and adequately monitor risk and benefit for marketed products such as medication error prevention and risk management plan review.

For the reasons mentioned previously—resources, communication, collaboration, leadership, and shared responsibilities—I do not believe that two separate and independent centers would improve FDA's ability to fulfill its mission to protect the public health.

Question 5. The Agency recently announced an overhaul of its advisory committee process. As you know, Senator Kennedy and I consider this an important issue, and we have proposed reforms to the process in our drug safety legislation. I don't want to work at cross-purposes with the FDA, so could you please tell me more about what you have planned? Do you believe that FDA can sufficiently improve the transparency and credibility of its processes with respect to advisory committee participation solely by administrative means?

Answer 5. In a speech given July 24, 2006, Deputy Commissioner Dr. Gottlieb discussed efforts to revise guidelines detailing the kind of industry ties that are permitted for those who serve on our advisory committees (see *http://www.fda.gov/oc/speeches/2006/conference0724.html*).

More specifically, we plan to revise the guidance documents used to determine how potential conflicts are evaluated, how waivers are granted, and how information regarding conflicts and waivers is disclosed. The goal is to make the process more transparent and clarify more of the case-by-case qualitative judgments we make when we evaluate each potential conflict. We do not plan to re-write existing rules, but instead, we intend to provide additional guidance and clarity regarding implementation of the existing statutory and regulatory framework regarding conflicts of interest. The revision process is currently underway and is a high FDA priority. We will make public the revised guidances as soon as they are completed.

We believe that these administrative changes will substantially improve the transparency of the process of managing our advisory committees, evaluating potential conflicts, and granting waivers where appropriate.

Question 6. The Nutrition Labeling and Education Act (NLEA) was enacted in 1990 to assist consumers in understanding the nutritional characteristics and ingredients in food and beverage items. I believe consumers need more and better information to make informed choices when purchasing foods and beverages for themselves and their families. It is my understanding that FDA is planning to re-evaluate the Nutrition Facts Panel (NFP) on food labels. Have you given any thought to requiring the disclosure of artificial sweeteners on the front of the package and listing the amounts in the Nutrition Facts Panel or additional labeling to help consumers distinguish between natural and artificial sweeteners?

Answer 6. FDA intends to issue an Advance Notice of Proposed Rule Making (ANPRM) to re-evaluate the Daily Values used in the Nutrition Facts panel based on recent recommendations from the Institute of Medicine Dietary Reference Intake and other scientific reports (e.g., 2005 Dietary Guidelines). This re-evaluation will be a comprehensive effort that will include a review of the Reference Daily Intakes (RDIs), which apply to vitamins and minerals, as well as the Daily Reference Values (DRVs), which apply to macronutrients. Sugars will also be addressed in the ANPRM.

Generally speaking, the Nutrition Facts panel (NFP) on conventional food labels contains nutrients of the type that have reference values; the only items in the NFP that do not currently have reference values are sugars and trans fat. Artificial sweeteners are not nutrients and thus do not have reference values. When used in foods, artificial sweeteners are required to be listed by common or usual name in the ingredients list. Thus, consumers can currently determine when artificial sweeteners have been used to sweeten a food product. In addition to the listing in the ingredient list, a manufacturer can provide statements elsewhere on the package about the type of sweetener used in the product as long as the information is truthful and not misleading.

Question 7. In August 2002, a number of organizations sent a citizen petition to FDA, asking that FDA revoke its approval of the abortion drug RU–486. The petition argues that FDA violated drug law and its own regulations and standards in approving RU–486 for medical abortion. FDA gave an interim response in June 2003. However, your agency has yet to give a final response. I would like to know when you intend to act on this petition, as we are now approaching the 4-year mark.

Please also tell me about what conclusions FDA, CDC and NIAID drew from the recent workshop on RU–486 and Clostridial infections. What are the next steps? It has been suggested that these unusual infections are not connected to the drug, but are instead an "emerging risk of pregnancy." What is FDA doing to make that determination?

Answer 7. In August 2002, three organizations (Concerned Women for America, Christian Medical Association and American Association of Pro Life OB-GYNs filed a citizens' petition requesting the FDA commissioner to stay the approval of Mifeprex "in light of legal violations and important safety concerns" and pending an audit (proposed by the petitioners) "of all records from the French and American clinical trials." FDA is still considering the numerous and complex issues raised in the citizen petition submitted in August 2002 as well as the supplement to the petition submitted in October 2003. Some of the concerns raised in the petition have been addressed through recent labeling changes and Dear Health Care Practitioner and Dear Emergency Room Director letters sent by the sponsor.

On May 11, 2006, in Atlanta, Georgia, Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and National Institutes of Health (NIH) jointly convened a public workshop entitled, "Emerging Clostridial Disease." The goal of the public workshop was to identify research needs and priorities to enable rapid progress in understanding the virulence, pathogenesis, host factors and non-antimicrobial risk factors contributing to reports of morbidity and mortality associated with *Clostridium difficile (C. difficile)* and *Clostridium sordellii (C. sordellii)*. The workshop resulted in a draft research agenda with recommendations for detecting cases and conducting surveillance of diseases and organisms.

As part of the meeting, it was anticipated that the three sponsoring agencies would publish proceedings of the workshop in a peer-reviewed medical journal. This is a time-consuming but important process that requires the focused participation of a number of individuals, and is being worked on at this time.

As part of the workshop, FDA expected to establish realistic time-lines for obtaining more knowledge on the pathophysiology and etiology of *C. sordellii* and determining whether regulatory action affecting the appropriate use and availability of these drug products is warranted. During the workshop, however, it became clear that understanding how and under what circumstances *C. sordellii* leads to clinical illness will be a daunting task. Research in this area is scant, and while the published cases of women who had recently undergone medical abortions are striking in their rapid, virulent course, they remain rare and unpredictable. Most importantly, it was clear from the workshop presentations that *C. sordellii* causes rapid and serious clinical illness in other settings as well, including among pregnant women who have recently undergone spontaneous abortion or term delivery. While there has been some speculation that certain immune-altering properties of mifepristone are the root cause of the cases reported in association with medical abortion, this is based primarily on *in vitro* data, and data to link *in vitro* properties of the drug to a single dose of the drug in humans are sparse. This point was made especially strongly at the inter-agency workshop by some of the most knowledgeable researchers in the field. It is also well known that pregnancy itself alters immune function from very early in gestation. The cases of infection in pregnant women who have not undergone medical abortion, as well as those who have, support the idea that pregnancy itself may be a plausible risk factor for *C. sordellii* illness.

At this time, FDA awaits the completion of CDC's study of maternal deaths in California as one set of data that may contribute to understanding the relative roles of pregnancy, mifepristone, other drugs, and other procedures to the occurrence of Clostridium illness. Nonetheless, it is unlikely that results from the study will definitively point to a specific cause of the infections and illnesses. Therefore, we have been and will continue to monitor adverse events associated with mifepristone, and will continue evaluating whether the labeling for Mifeprex, including the Medication Guide that is required to be given to patients, will need to be updated to ensure that available safety information is clearly communicated to both healthcare providers and patients.

We offer the following Website as a source for further details on the workshop: *http://www.fda.gov/cder/meeting/clostridia*__disease.htm.

Question 8. During the last reauthorization of the drug user fee law, FDA was instructed to come up with a 5-year strategic plan for information technology. In addition, there are numerous efforts across the Department of Health and Human Services to move toward interoperable platforms and electronic health records. However, we are still hearing that the IT infrastructure at FDA may be inadequate to meet the Agency's mission. What is the status of the strategic plan? Are you meeting the milestones set out under the plan? What resources are still needed?

Answer 8. FDA met all the goals of the PDUFA III 5-year IT strategic plan. We established an IT shared services organization, developed service level agreements, and implemented a consolidated call center, to improve efficiency and effectiveness and provide a one-stop shop for some IT services.

Although the PDUFA III legislation mandated publication of only a 2003–2007 IT strategic plan, FDA honored the spirit of the legislation through a process of continual improvement. We implemented a data center consolidation effort to reduce the number of FDA data centers from six to the current three and eventually to two, reducing the staff and facilities needed to operate our infrastructure. We are in the process of a hardware consolidation project, to allow us to move as little hardware as possible under the data center consolidation, and to retire the oldest hardware to save on maintenance costs. We are also using some new software and processes to better manage our IT resources.

FDA also invested in selected portions of its hardware infrastructure to accommodate the highest priority initiatives. The completed FDA Electronic Submissions Gateway allows for the secure submission of regulatory documents over the Internet. HHSMail, one of many departmentwide efforts in which FDA participates, is on track to provide robust e-mail capability in fiscal year 2007.

Question 9. There has been a lot of focus lately on the number of generic drug applications pending at the Agency. The number that gets mentioned a lot is 800 pending applications. My understanding is that about a quarter of these are known as Paragraph III certifications, which means that FDA couldn't do anything to speed the product to market, since the patent hasn't expired yet. Is this correct? If so, that reduces the number, but still leaves a large number of applications in the queue. Can you tell me what FDA is doing to shrink the backlog? A number of blockbuster medications are going to lose patent exclusivity over the next couple of years. How will FDA be able to speed generic versions of those drugs to market, if it doesn't first take care of the backlog?

Answer 9. It is correct that approximately one fourth of the applications in the backlog are paragraph III applications. We should also point out that the backlog, as traditionally defined, includes ANDAs cycling through our Office of Generic Drugs (OGD) during second and subsequent review cycles. In some cases, the applicant does not respond to these deficiencies in a timely manner due to their own resource limitation and priorities, which contributes to the backlog.

FDA has taken significant steps to improve our resources. Total spending on the Generic Drug Program is $64.6 million, which is more than a 66 percent increase from the comparable fiscal year 2001 amount. FDA has increased its generic drugs full-time equivalent (FTE) positions from 134 in fiscal year 2001 to 201 in fiscal year 2006.

Last year, FDA added 12 new FTE positions to OGD's staff. These individuals, now fully trained, have recently reached the point in their learning curve where they are now full contributors to the efforts of OGD. In addition, OGD has taken actions to streamline the ANDA review process. These actions include adding a third chemistry review division and a fifth team in OGD's Division of Bioequivalence. Also, a number of new review practices have been implemented to improve interactions with generic drug companies. We have begun utilizing nonreviewer Project Management staff to take certain actions not requiring scientific expertise, thus alleviating the burden of these activities on the review staff. OGD has instituted other efficiencies to application review.

Other efficiencies we have implemented include:

- Reviewing Drug Master Files (DMFs) prior to the time the related ANDAs are assigned since the DMF evaluation is often the limiting factor in completing the ANDA review.
- Utilizing telephone conversations with ANDA sponsors, when appropriate, to resolve deficiencies more efficiently and expeditiously.
- Assigning applications to reviewers with related expertise or experience with a particular drug class.
- Utilizing a new format for the chemistry review called question-based review. It is based on the structure of the International Conference on Harmonization Common Technical Document for the chemistry review.
- Utilizing a team review approach for "clusters" of applications for the same product.

Because of these efforts, OGD has been able to issue final approvals on most applications when the last applicable patents or exclusivities blocking approval expire. If there are no products eligible for 180-day exclusivity, OGD has usually been able to approve two or more applications for the same product. Recent examples of approvals when the patents expired include pravastatin (Provachol); sertraline (Zoloft);

and simvastatin (Zocor). On July 19, 2006, multiple applications for meloxicam (Mobic), a product with no patent or exclusivity protection blocking approval, were approved. Using OGD's "cluster" team approach, these applications were approved in just over 9 months. These approvals will result in generic products available for patients potentially saving millions of dollars in medication costs.

Question 10. In the fiscal year 2007 Budget proposal, there was a "strategic redeployment" of funds within the Agency to address priority needs. These funds largely came from the Center for Food Safety and Nutrition, a very important part of FDA. I was relieved to see that most of these cuts are likely to be restored during the appropriations process. I am a strong supporter of wringing efficiencies out of the budget, but I am concerned that food safety is not considered a high enough priority. This concern was echoed this July during a HELP Committee hearing on food uniformity. Could you comment on the proposed redeployment and how the Agency will continue to support its mission in those areas? Can FDA expand its efforts with the resources available?

Answer 10. The strategic redeployment associated with the President's fiscal year 2007 budget will allow the Agency to fund six critical high priority initiatives: pandemic preparedness, food defense, drug safety, critical path to personalized medicine, human tissues and budget authority to ensure we meet the devices and animal drug user fee triggers. Food safety is another high priority initiative for FDA. The Agency will continue to meet its food safety obligations by employing a risk-based approach, which relies on the Agency's strategic planning process to focus resources on high-risk public health challenges while maintaining our century-old commitment to principles that have made FDA the world's "gold standard" for regulating food and ensuring food safety.

Question 11. I've 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 hasty or unwise decisions to approve drugs. Do you agree with this perspective? Please explain to the committee: (1) the importance of PDUFA and the way you will ensure, as Commissioner, that (2) there will continue to be no compromise of FDA's standards in reviewing products covered by user fees.

Answer 11. FDA has established and continues to operate under stringent criteria for scientific and regulatory review of drug products and biologics, no matter the source of funding.

PDUFA authorized FDA to collect fees from companies that produce certain human drug and biological products. Previously, taxpayers alone paid for product reviews through budgets provided by Congress. In PDUFA, industry provides funding in exchange for FDA agreement to meet drug-review performance goals, which emphasize timeliness.

PDUFA funds allowed FDA to accomplish a number of important goals. FDA hired more review and support staff to speed review. The number of full-time equivalent (FTE) staff devoted to the new drug review process has nearly doubled, growing from 1,277 FTE in 1992 to 2,503 FTE in 2004. FDA upgraded its data systems and gave industry guidance to help minimize unnecessary trials and generally improve drug development. FDA gave industry guidance on how to improve the quality of applications, with the goal to reduce misunderstandings and the need for sponsors to rework and resubmit applications. Finally, FDA improved procedures and standards to make review more rigorous, consistent, and predictable.

Since PDUFA's inception, FDA has met or exceeded all PDUFA NDA and BLA review goals. Between 1993 and 2003 the median approval time for priority NDAs and BLAs decreased by over half—from 13.2 months in 1993 to 6.4 months in 2003. Over this same time period the median approval time for standard NDAs and BLAs decreased by over one third, from 22.1 months in 1993 to 13.8 months in 2003.

Additional PDUFA goals specifically focused on preserving an appropriate balance between drug efficacy and drug safety by funding safety-related activities for the first 2 years of product marketing for most drugs, and the first 3 years for potentially dangerous drugs. PDUFA fees also enabled FDA to issue guidance for FDA and industry on how best to assess, manage, and monitor drug risk. Additional details can be found on our Website: *http://www.fda.gov/oc/pdufa/default.htm*.

Question 12. Public health officials, physicians and scientists alike are increasingly concerned about the likelihood of a flu pandemic. Though not of terrorist origin, a flu pandemic would be a biomedical catastrophe that could seriously compromise homeland security, through its impact both within and outside this country. Vaccines will be the key part of our response to a flu pandemic. However, scientific, legal, and economic considerations have led to a shrinking domestic vaccine indus-

try. What more can FDA do to prepare for a flu pandemic? How could Congress and FDA best work together to rebuild our vaccine capacity?

Answer 12. FDA has worked to streamline the vaccine approval and licensing process to encourage new vaccine development and make vaccines available sooner. In March 2006, the Agency published two draft guidance documents to aid manufacturers in developing vaccines for both seasonal and pandemic influenza. The guidances recommend specific approaches that vaccine developers can follow to provide evidence of the safety and effectiveness of new vaccines. Additionally, the guidances provide information on flexible, regulatory pathways for getting vaccines to market. One of these pathways is the accelerated approval process that can substantially reduce the time for the development of a new vaccine. Because these guidances assist manufacturers in the development and evaluation of new vaccines for seasonal and pandemic influenza, they will help address the increased demand for vaccine.

Having additional manufacturers will enhance the capacity to produce more doses of influenza vaccine every year, and contribute to the Nation's pandemic preparedness as well as provide better protection against failures of single manufacturers. To this end, FDA contacted major manufacturers of influenza vaccine throughout the world to stimulate interest in producing vaccine for the U.S. market. This outreach resulted in one additional vaccine product approval for the 2005–2006 season, helping to prevent a significant shortage. We continue to work with additional manufacturers to encourage them to enter the U.S. market, a potentially important step in helping increase and diversify the supply of flu vaccine in future flu seasons. For example, ID Biomedical of Canada recently submitted a U.S. license application for its flu vaccine.

FDA is also undertaking efforts to facilitate development of influenza vaccines using new technologies, including cell-based, and other novel types such as DNA and synthetic peptide. The Agency will continue to work with Congress to address the critical need for a dependable supply of influenza vaccine.

Question 13. I have heard a lot this year from all sides regarding the use of carbon monoxide (CO) in "case ready" meat. It seems to me this debate hinges on whether CO is a food additive or a color fixative. Could you please explain to me the statutory and regulatory differences between a food additive and a color fixative, and how FDA made the determination that CO is a color fixative?

Answer 13. One of the issues that has been raised on the use of carbon monoxide (CO) in "case ready" meat is whether CO should be considered a color additive under the statute for this use. This distinction is important because, under the statute, the use of a color additive is unlawful unless it is subject to pre-market review and approval and is listed in the Code of Federal Regulations; there is no generally recognized as safe (GRAS) exception from this requirement in the case of a color additive as there is for food additives.

The Federal Food, Drug, and Cosmetic Act defines a color additive, in part, as a substance that when added to food ". . . is capable . . . of imparting color thereto." During its review of the GRAS notifications for the use of CO in modified atmosphere packaging for meat, the Agency concluded that the CO did not "impart" color, but rather maintained the red color of the meat. As a color "fixative" rather than a color additive, this use of CO may be GRAS, which exempts the CO from the requirement for approval and listing by FDA.

FDA has received a petition stating that the Agency should have classified this use of CO as a color additive; the Agency is currently reviewing the petition and will respond as soon as possible.

Question 14. On June 8, 2006, FDA released a final Compliance Policy Guide regarding unapproved prescription drugs. Many of the drugs that fall under this category have been marketed for many years and used in thousands, if not millions, of patients without significant safety issues. However, some of these drugs do have safety issues, and I am concerned about how FDA's enforcement resources are being prioritized. Please describe for me how FDA is prioritizing the regulation and enforcement of these drugs.

Answer 14. FDA takes seriously the threat posed by drugs that have not been subject to FDA's rigorous scientific review before being provided to patients. Because many of these unapproved drugs have been around for a long time, some people presume that these drugs are safe and effective. But, unapproved drugs may not be safe and effective, and their manufacturing quality and labeling also may not meet modern standards necessary to protect public health.

The final Compliance Policy Guide (CPG) entitled, "Marketed Unapproved Drugs," issued by the FDA on June 8, 2006, outlines a risk-based enforcement approach that is flexible, but firm, and includes the identification of illegally marketed drugs, the

prioritization of those drugs based on their potential to harm the public health, and subsequent regulatory followup.

The guidance articulates FDA's expectation that manufacturers of products requiring FDA approval submit new drug applications to FDA to show that their products are safe and effective. The guidance also outlines the Agency's enforcement policies. As described in the CPG, the highest priorities for enforcement action will continue to include drugs with potential safety risks, drugs that lack evidence of effectiveness, and health fraud drugs. This CPG is available online at: *http://www.fda.gov/cder/guidance/6911fnl.htm*.

FDA has been focused on addressing the threat of unapproved drugs problem as one part of our broader drug safety initiative, announced last year, to ensure that patients, consumers, and health-care providers have the most up-to-date drug safety information.

Question 15. FDA regulations permit any interested party to submit a citizen petition to the Agency requesting, among other things, the FDA to issue, amend or revoke a regulation or to take or refrain from taking a particular action. I understand that FDA has been reviewing its citizen petition process. However, 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? If the use of citizen petitions was limited, as some have proposed, wouldn't that also limit the mechanisms through which the public can comment on a pending FDA action?

Answer 15. The Center for Drug Evaluation and Research (CDER) is responsible for responding to citizen petitions relating to certain drug products, including generic drugs. Within CDER, the Office of Regulatory Policy (ORP) has primary responsibility for drafting responses to citizen petitions, except for petitions relating to over-the-counter drug monographs or "suitability" petitions (see 21 CFR 314.93). Recently, CDER has seen a significant increase in petitions. For example, ORP saw a 50 percent increase in petitions received in calendar year 2004 over calendar year 2003, and in calendar year 2005 ORP received 65 petitions, nearly the calendar year 2004 total of 70. For calendar year 2006, we anticipate a greater increase because ORP received 53 petitions as of July 31. This increase includes not only citizen petitions relating to Abbreviated New Drug Applications (ANDAs) or generic drug applications, which involve the Office of Generic Drugs (OGD), but also an increasing number of petitions raising drug safety issues handled by other parts of CDER.

In response to the increase in petitions and an increasing backlog of pending petitions, ORP initiated an extensive review of processes for responding to petitions. As a result, CDER instituted a number of changes, including:

- ORP has been increasing its early interactions with other offices to better coordinate responses.
- All parties involved in responding to petitions have attempted to increase communications to avoid misunderstandings, wasted efforts, or unnecessary delays.
- ORP and the OGD regularly discuss priorities and anticipated timetables, so responses can be coordinated with ANDA approval actions.

In addition, OGD has made organizational changes to improve the petition response process. OGD has dedicated a group of highly skilled scientists to address complex scientific issues related to review of ANDAs and citizen petitions. This change is expected to increase the consistency, quality and speed of OGD's input on petition responses.

Although much of the focus on the citizen petition process has been on challenges to the approval of generic drugs submitted to the Agency in citizen petitions, the Agency also receives scientific and legal challenges in correspondence sent directly to OGD and to other offices in the Agency, and in submissions to applications. As with citizen petitions, if the issues raised relate to the approval requirements for an ANDA, the Agency must address the issues raised in the submission to determine whether the pending application meets the statutory and regulatory requirements for approval.

Question 16. In December of last year, the FDA announced the results of an operation that examined prescription drugs entering our borders via personal importation. According to the FDA press release, of the parcels that FDA examined that claimed to be Canadian, 85 percent actually came from 27 countries around the globe. You stated in the press release that these results make clear there are Internet sites that claim to be Canadian that are in fact peddling drugs of dubious origin, safety and efficacy. This seems to coincide with recent public statements made by so-called Canadian Internet pharmacies which have stated they are filling 50 percent of their prescriptions from foreign countries. Can you describe the analysis

FDA conducted last year of drugs entering our borders and whether you still have concerns regarding importation, even if limited only to drugs imported from Canada?

Answer 16. FDA remains concerned about drug importation by American consumers. There is no evidence that drugs purchased by consumers directly from foreign sources are safe and effective or that these drugs have been produced under FDA's current good manufacturing practice standards. American consumers often seek out Canadian suppliers because they believe them to be reliable. However, we have found that many "Canadian" sources falsely purport to be Canadian and/or many of the drugs purchased are not even of Canadian origin. An FDA effort last year (referred to as "Operation Bait and Switch") confirmed these findings.

Operation Bait and Switch was designed to examine mail parcels imported into the United States containing pharmaceuticals that claim to have originated from Canada, and to provide an overall assessment of the quality, identity and potency of these pharmaceutical products.

FDA evaluated the admissibility of the parcel contents coming from India, Israel, Costa Rica, and Vanuatu (an island in the South Pacific), photographed the parcels and contents, captured the Canadian link information (i.e., Website, firm name, province), collected samples for analysis, and entered the parcel/product data elements (i.e., firm name, product, web address) into FDA's import database.

Analysis showed that about 43 percent of the parcels were ordered from "Canadian" Internet pharmacies and were represented as being of Canadian origin. However, only 15 percent of these parcels examined actually originated in Canada. The remaining 85 percent were manufactured in 27 different countries. FDA selected products that met the following criteria (based on the "Orange Book" approval status of each product) and then performed assay and identification testing:

1. The active ingredient of the drug or drug combination itself was unapproved for sale in the United States; or
2. The dosage strength of the drug was unapproved for sale in the United States; or
3. The drug was approved for sale in the United States, but the manufacturer was not an approved manufacturer of the drug.

In addition to assay and identification testing, frequently counterfeited products were analyzed for authenticity. Techniques used included visual analysis (macroscopic and microscopic) and chemical analysis (impurity/inactive ingredient profiling). Results of the sample analyses showed sub-potent, super-potent, and counterfeit drugs.

Further, even for drugs obtained from a Canadian source, we still cannot be certain that the drugs are identical to those approved by the FDA; they could in fact be counterfeit. Also, since Canadian drugs are not subject to FDA scrutiny and have moved about in a foreign distribution system, they could have been stored under improper temperatures, or subject to tampering or other interventions that could cause them to be unsafe.

Question 17. With the recent expiration of patents on a handful of blockbuster drugs and more coming in the next year, there has been greater attention focused on the issue of authorized generics. Some studies have shown that there are consumer benefits to authorized generics, because they increase competition and can drive down the price of drugs. Others have suggested that authorized generics in fact create disincentives to entering the market. This issue has gained attention from Congress and the Federal Trade Commission has asked for public comments on a proposed study.

As you know, the FDA has in the past denied citizen petitions requesting that FDA prohibit the marketing and distribution of authorized generics until after the 180-day exclusivity period. This decision by FDA has subsequently been upheld by the courts. Can you describe FDA's basis for its decision?

Answer 17. As you know, under the 1984 Hatch-Waxman amendments to the Federal Food, Drug, and Cosmetic Act, the first generic drug applicant to submit an abbreviated new drug application (ANDA) that challenges the validity or applicability of a patent claiming the brand name drug is eligible to receive 180 days of marketing exclusivity, during which it may be the sole manufacturer to obtain approval of an ANDA for a generic version of the brand name drug.

Citizen petitions filed by two generic drug companies sought, in essence, to extend this marketing exclusivity to also prevent competition during the 180-day exclusivity period from "authorized generics" (lower-priced versions of the innovator drug itself, marketed by or for that innovator company and marketed pursuant to the innovator's approved NDA). Innovator companies are increasingly engaging in this type of competition.

The Agency denied the two petitions because it concluded that, although it must refuse to approve any other ANDA for the same generic drug during the 180-day exclusivity period, FDA does not have the statutory authority to prohibit the marketing of authorized generics, because these drugs are marketed subject to the innovator manufacturer's approved new drug application (NDA), not pursuant to an ANDA. The Courts of Appeals for the District of Columbia Circuit and the Fourth Circuit have upheld the Agency's decision.

Question 18. When it comes to drugs, I have heard the argument that children are not mini-adults. In other words, we cannot assume that because a medicine behaves one way in the body of an adult, it will have a similar effect in a child. I understand that conducting trials in children raises a number of ethical issues and scientific complexities and the costs for conducting pediatric research is likely to climb in the next decade as requirements expand and there is greater difficulty in recruiting. However, I do believe we have some success stories to tell in this area. Next year, we will reauthorize both the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. Please summarize the status of FDA's activities under these two laws.

Answer 18. As of August 1, 2006, under the exclusivity provisions of the Best Pharmaceuticals for Children Act (BPCA) and the Food and Drug Administration Modernization Act (FDAMA), FDA has issued 323 Written Requests and made 135 exclusivity determinations for studies submitted in response to the Written Requests. Pediatric studies conducted under those provisions have resulted in 114 labeling changes. Summaries of study reviews have been posted for 64 drugs. The number of exclusivity determinations differs from the number of summaries posted because the authority to post the reviews was granted under BPCA, and the 135 exclusivity determinations are cumulative since the passage of FDAMA. In general about 25 percent of the products that were being used in children that were studied under these incentive programs have gained new dosing or safety information in addition to data on efficacy in a new age group as a result of these pediatric studies. Important new information has been developed on antivirals for HIV in the neonatal population; drugs for the treatment of cancers in children; drugs for the relief of pain resulting from cancer and its treatment, as well as from the severe nausea that occurs with chemotherapy; and drugs for asthma, a disease that is becoming more prevalent in the United States and which can result in sudden acute attacks and possibly death in children.

Following enactment of BPCA, the Office of Pediatric Therapeutics (OPT) was established within the Office of the Commissioner. OPT has five mandated areas of responsibility: pediatric ethics and coordination of Subpart D referrals for public review by the Pediatric Ethics subcommittee (PES), safety reviews and reporting to the Pediatric Advisory Committee (PAC), agency-wide scientific coordination of pediatric issues, external communications with pediatric stakeholders and international colleagues, and program management of the PAC. One year post-exclusivity adverse event reports have been presented on 54 drugs at 9 meetings of the PAC, all coordinated by OPT. In addition, there have been 3 Subpart D referrals, 6 meetings of the PES and numerous consultations on the ethical conduct of studies in children. The ethicist in the Office of Pediatric Therapeutics, a newly created position mandated by BPCA, has provided over 80 consults on trial design issues and related questions. In addition there were 10 pediatric scientific issues brought to the PAC for discussion between 2002–2005.

FDA has also seen significant improvements in labeling for pediatric populations due to studies conducted under the Pediatric Research Equity Act (PREA). Preliminary numbers indicate that, for applications that were submitted to CDER since April 1, 1999, 286 applicants have fulfilled their pediatric studies requirements under PREA. CDER has granted 570 waivers of pediatric studies and 429 deferrals of pediatric studies pursuant to PREA provisions. We are now in the process of compiling labeling changes that resulted from PREA studies and expect to be able to publicly post these labeling changes to the pediatric Website by the end of this year. The Center for Biologics Evaluation and Research (CBER) had 16 approved Biologics License Applications (BLA) and Biologics License Supplements (BLS) submissions received from April 1, 1999 through August 21, 2006 which included the complete required pediatric studies. Since April 1, 1999, CBER has granted 24 deferrals and 5 waivers.

Question 19. This past January, voluntary principles on direct-to-consumer (DTC) advertising went into effect. In addition, FDA has stated that ads are doing a better job weaving together discussions of risks and benefits. I believe responsible direct to consumer advertising should inform and educate patients about treatable condi-

tions and available therapies. I think things are getting better, but I am still concerned 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, or educate patients about various treatment options and the risks associated with those options.

Do you generally believe in the merits of DTC advertising and in its role in educating and empowering patients? Are you encouraged by the direction these ads seem to be heading in recent months? How can we ensure consumers get the best of DTC advertising?

Answer 19. We believe direct-to-consumer (DTC) advertisements can play an important role in advancing the public health by encouraging consumers to seek treatment for diseases that may be under-treated and diseases for which consumers may not be aware treatment options exist. We continue to monitor the impact of consumer-directed promotion on the public health.

Following the implementation of "PhRMA's Guiding Principles on Direct to Consumer Advertisements about Prescription Medicines" in January 2006, FDA reviewers of DTC ads are encouraged by improvements in some consumer-directed advertisements. Some companies are making an effort to more fully integrate risk messages into ads and to work to achieve a tone that does not minimize the serious nature of prescription drugs. We believe the principles issued by the Pharmaceutical Research and Manufacturers of America (PhRMA) are a positive development, and we are pleased that PhRMA is taking steps to address several of the problems associated with DTC advertising. We agree with the concepts in PhRMA's principles that: DTC promotion should truthfully and accurately convey the benefit and risk information about products; PhRMA's member companies should fully comply with the applicable laws and regulations; DTC ads should respect the seriousness of the advertised medical condition and the importance of the relationship between the patient and healthcare provider; and companies should be encouraged to promote disease and health awareness as part of their DTC advertising. In our opinion, however, it is too soon to tell whether there has been a real and lasting shift in the DTC environment.

The Agency believes that consumers can receive the best information from DTC advertising when companies comply with FDA's regulations and promotion is accurate, nonmisleading, and presents a fair balance of information about the benefits and the risks of the product. It is very important that companies present information in clear, understandable and nontechnical language. Efforts by pharmaceutical companies to promote disease and health awareness are very important, particularly for conditions that are under-diagnosed and under-treated in the population.

Question 20a. In recent weeks, I have been contacted by Rebecca Painter, a capable and respected physician from my home town of Gillette, and by numerous Wyoming patients regarding mercury in dental amalgam. My conversations with her have raised a number of questions.

FDA allows devices on the market either by the manufacturer demonstrating safety and efficacy (a "pre-market approval" application, or PMA) or by a truncated method (a "pre-market notification," also known as a 510(k)). For dental amalgam, FDA used the latter system. Can you explain the basis for FDA's decision to allow marketing of dental amalgam under the 510(k) process? What was the "predicate device" used for dental amalgam?

Answer 20a. The medical device provisions of the Food, Drug, and Cosmetic Act have two systems to allow for marketing of medical devices, the pre-market approval system and the pre-market notification system. PMA devices are almost always devices classified into Class III; they often involve new concepts and many are not of a type marketed prior to the 1976 Medical Device Amendments. A 510(k) is a pre-marketing submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent (SE), to a legally marketed device that is not subject to pre-market approval (PMA). Applicants must compare their 510(k) device to one or more similar devices currently on the U.S. market and make and support their substantial equivalency claims. A legally marketed device is a device that was legally marketed prior to May 28, 1976 (pre-amendments device), or a device which has been reclassified from Class III to Class II or I, a device which has been found to be substantially equivalent to such a device through the 510(k) process, or one established through the "de novo" process, which allows down classification of devices automatically classified into class III. The legally marketed device(s) to which equivalence is drawn is known as the "predicate" device(s). Dental amalgam devices are pre-amendments devices, that is, they were on the market prior to 1976 when the medical device amendments were instituted. In addition the Dental Products classification panel that met between 1976 and

1978 classified dental amalgam devices. Dental Mercury was classified as class I and amalgam alloy was classified as class II.

Question 20b. A Zogby poll in 2006 indicated that less than one in four Americans can identify mercury as the main component of dental amalgam. This may be due in part to its nickname, "silver fillings." What does FDA do to help consumers understand the composition of dental amalgam so they can make an informed choice?

Answer 20b. In our February 20, 2002 proposed reclassification of dental amalgam devices we proposed ingredient labeling, such that all components would be listed on the device. This would be very different from other medical devices, in that ingredient labeling is not required by law or regulation. Although the reclassification has not been finalized, there is a Consumer Update on our FDA/CDRH Website *http://www.fda.gov/cdrh/consumer/amalgams.html*.

Question 20c. Most people would probably want to reduce their mercury exposure, and there are a number of ways to work toward this. Manufacturers of many mercury-containing products are voluntarily reformulating their products to use a non-mercury-based preservative. FDA has taken action regarding some products containing mercury. For example, in 1998, it banned mercury in wound disinfectants, such as Mercurochrome. Finally, other countries are also acting. Health Canada has recommended against pregnant women and children receiving fillings with mercury-containing dental amalgam. Does FDA have any plans to make a similar recommendation? If not, why not?

Answer 20c. FDA has based its regulation of dental amalgam products on scientific reviews of the literature in 1993, 1997 and other peer-reviewed literature. None of these reviews of the literature have found studies showing that adverse health effects occur as a result of dental amalgam restoration use, except potentially in individuals with allergic reactions to mercury. We have also compared estimated mercury exposures from dental amalgam restorations to health-based comparison values established by EPA and ATSDR which explicitly consider sensitive populations such as women and children. These comparisons also do not indicate that adverse health effects are likely as a result of dental amalgam restoration use. We continue to look at the literature to determine if there is additional information that would cause us to change our view. We will again in September 2006, during a joint CDER Neurology panel and CDRH Dental panel meeting, look at the peer-reviewed scientific literature relevant to consideration of health effects for dental amalgam restoration use. Any new information that has been published since 1997 will be discussed at this meeting.

Question 20d. In September, FDA will host a joint committee meeting to, quoting from your announcement, "review and discuss peer-reviewed scientific literature on dental amalgam and potential mercury toxicity, specifically as it relates to neurotoxic effects." I believe this is the first time FDA has held such a hearing, and I commend you for your leadership on this issue. The general function of this joint committee is listed as "to provide advice and recommendations to the agency . . .", but the agenda simply lists review and discussion of scientific literature. Will the joint committee be specifically charged with making recommendations? If they make recommendations, will you carry out those recommendations?

Answer 20d. We do have a panel meeting scheduled in September 2006 to discuss this topic. However, this is not the first time that FDA has held such a meeting. In 1993–1994, the Dental Products panel also discussed the regulation of dental amalgam, and we received classification recommendations from that panel. The September panel will be asked to answer specific questions concerning any possible adverse health effects of dental amalgam. The proceedings and recommendations of the panel will be considered by FDA in our regulation of dental amalgam devices.

Question 21. In October 2005, FDA proposed an additional rule to prohibit certain high-risk material from all animal feeds and pet foods. What is the status of this regulation?

Answer 21. FDA has considered approximately 800 public comments submitted in response to the October 2005 proposed rule. FDA has completed its analysis of these comments, and significant progress has been made in drafting the final rule. A number of comments dealt with the economic costs and potential environmental consequences of the proposal and noted that FDA had not adequately considered these impacts. The new information has caused FDA to reconsider the underlying assumptions on which the economic and environmental impacts were based in the proposed rule. As a result, we are currently completing a detailed re-analysis of the economic and environmental impacts of the proposal in light of the comments and other new

information that has become available. Though this re-analysis has caused some delay, FDA plans to develop and issue a final rule as expeditiously as possible.

Question 22. Among the Agency's 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. These programs are sometimes called compassionate use or expanded access programs. There is also a pending Citizen Petition on reform of these programs. Patients dying from terminal diseases think this regulation should be among the FDA's highest priorities. What is the status of this regulation and when will the draft regulation be published in the Federal Register?

Answer 22. Publication of rules on expanded access to investigational drugs (Expanded Access to Investigational Drugs and Treatment Use and Charging for Investigational Drugs) remains a very high FDA priority. As is our longstanding policy, we are unable to comment publicly on the specific clearance status of rules. Moreover, it is quite difficult to predict publication dates due to multiple steps in the review process. It is also too early for us to accurately revise the publication date estimate for these rules that will appear in the next Semi-annual Regulatory Agenda to be published this fall. As noted, FDA continues to treat these important rules with the highest priority, and remains committed to their publication at the earliest possible time. I also want to stress that even as we work on these clarifying rules, there are expanded access programs in place to provide access to needed drugs for persons with serious and life-threatening diseases.

Question 23. Some electronic products are regulated by both FDA and OSHA. Please tell me about how you work with OSHA to establish uniform standards for these products, eliminate duplication of regulatory efforts, and maximize resources used to assure compliance.

Answer 23. FDA and OSHA avoid duplication of regulatory efforts because they regulate different aspects of the same products. FDA regulates the manufacturers of electronic products. Under authority of Sections 531–542 of the Federal Food, Drug, and Cosmetic Act, FDA promulgates and administers radiation safety performance standards for electronic products that generate ionizing, nonionizing, sonic, or particulate radiation. The FDA standards recognize that some electronic products may emit hazardous radiations that are necessary for their intended functions, and require controls, indicators, and warnings appropriate to the level of the hazard. OSHA regulates employers and evaluates their control measures in place to protect workers using or near the products. For example, for laser products, the FDA enforces the laser product radiation safety performance standard at 21 CFR Part 1040, and OSHA uses the ANSI Z136 series (American National Standards for the Safe Use of Lasers) of user standards as the basis for its determinations.

FDA and OSHA also work together to write Federal guidance and voluntary radiation safety consensus standards for electronic products. Current projects include:

- An Interagency Steering Committee on Radiation Standards (ISCORS) work group drafting "Guidance for Security Screening of Humans Utilizing Ionizing Radiation";
- An American National Standards Institute (ANSI) work group updating N43.17 Radiation Safety of Personnel Security Screening Systems; and
- An ANSI work group drafting N43.16 Radiation Safety for X and Gamma Radiation Security Inspection Systems.

Question 24. In December 1999, FDA published regulations implementing provisions of the Prescription Drug Marketing Act (PDMA) regarding the wholesale distribution of drugs that set forth requirements regarding pedigrees. The FDA has stayed that regulation a number of times. Earlier this year, FDA announced that the stay would be lifted, and the regulation would go into effect on December 1, 2006. Given what we have heard about counterfeiting and diversion of pharmaceuticals, I am very pleased that the Agency is moving forward on this. However, I am concerned that simply lifting the stay may not really solve the problem. This regulation does not fully take into account new technologies, such as RF–ID, and was written in a pre-9/11 world. Can you tell me more about how FDA will implement this regulation in a modern, effective way?

Answer 24. In February 2004, FDA delayed the effective date of certain provisions of regulations that implement the PDMA's pedigree requirements (21 C.F.R. §§ 203.3 (u) and 203.50) for the distribution of drugs until December 1, 2006, in part, because we were informed by stakeholders in the U.S. drug supply chain that the industry would voluntarily implement electronic track and trace technology by 2007. If widely adopted, this technology could create a *de facto* electronic pedigree

that would document the sale of a drug product from the place of manufacture through the U.S. drug supply chain to the final dispenser. Although, progress has been made, it appears that the use of electronic track and trace technology, including RFID, will not be widely adopted by 2007. The issue of developing technologies was explored at FDA's public workshop in February 2006.

Following the public workshop, FDA announced in June 2006 that it did not intend to further delay the effective date of §§ 203.3(u) and 203.50 beyond December 1, 2006, and that the stayed regulations will go into effect on that date. At the same time, FDA issued a draft Compliance Policy Guide to clarify for FDA personnel and the regulated industry how the Agency intends to prioritize its enforcement efforts during the next year regarding the pedigree requirements. Given the absence of widespread implementation of electronic pedigree technology to date and the continuing threat to public health as described in the *FDA Counterfeit Drug Task Force Report: 2006 Update*, the Agency determined that lifting the stay is the best method of protecting the public health and meeting the mandates of the PDMA. The Agency is hopeful that the implementation of these regulations may spur the development and adoption of electronic track and trace technologies.

Furthermore, FDA has received a number of questions from stakeholders about complying with the regulations and is working on a document to address these questions. We believe that this document may address your implementation concerns as well.

RESPONSE TO QUESTIONS OF SENATOR KENNEDY BY ANDREW C. VON ESCHENBACH

Question 1a. Could you please describe the "enforcement considerations" referred to in your July 31 letter that warrant allowing Plan B over-the-counter status only for women 18 and older, and not 16 and older, or 17 and older?

Answer 1. In considering the difficulty of enforcing an age-based restriction on the availability of this oral hormonal contraceptive, I have concluded that 18 (rather than 17) is the more appropriate cutoff to best promote and protect the public health. The state-regulated pharmacies that will be dispensing Plan B® under Barr's voluntary Convenient Access, Responsible Education (CARE) program are accustomed to the age 18 as a cutoff age for access to restricted products. I understand that in all 50 states, 18 is the age of majority (i.e., the legal delineation between minor and adult), and retail outlets, including pharmacies, are familiar with using 18 as the age of restriction for the sale of certain products. With regard to drug products, for example, the legal age to purchase FDA approved non-prescription nicotine replacement therapy products is 18. Moreover, I understand that as a matter of State law, many products routinely sold by pharmacies, e.g., tobacco products and nonprescription cough-cold products like pseudoephedrine are restricted to consumers 18 and older. The approach builds on well-established State and private sector infrastructures to restrict certain products to consumers 18 and older.

Question 1b. Could you also please point to those portions of the summary of the comments on the Advanced Notice of Proposed Rulemaking in which this age limit is discussed?

Answer 1b. The Advanced Notice of Proposed Rulemaking (ANPRM) which published on September 1, 2005 included a section titled "Agency Request for Information." Question 2 of the ANPRM asked for comments on limiting sales of an over-the-counter (OTC) product to a particular subpopulation. This question generated comments which addressed various age subpopulations.

The issue outline developed to assist in categorizing and summarizing the ANPRM comments broke Question 2 down into several areas. The two main issue areas were identified as: (1) "If FDA Limited Sale of OTC Product to Sub-population, Would FDA be Able to Enforce Limitation as a Matter of Law?" and (2) "Would FDA be Able to Enforce Limitation to Sub-population as a Practical Matter?" These two questions were further divided into sub-issue areas to categorize comments that provided legal or policy arguments and the actions FDA could or could not take to enforce a specific limitation to a particular subpopulation. Included in the comments to the ANPRM were comments that discussed age limits.

Question 2. Your July 31 Plan B letter also indicates that to get Plan B approved OTC for women 18 and over, the manufacturer needs a plan that is "sufficiently rigorous" and that will "prevent" younger women from getting the drug without a prescription.

I don't believe restrictions on distribution for other drugs are expected to "prevent" safety concerns presented by the drug. Rather, I think the idea has been to reduce and minimize risks. Moreover, the limitations are supposed to be commensurate with the specific safety concerns presented by the drug.

Please compare what you are looking for with what is required for other drugs with restrictions on distribution and use. In addition, what are the specific safety concerns presented by Plan B, and compare them to the safety concerns with other drugs with restrictions on distribution and use.

Answer 2. On August 24, 2006, FDA approved Plan B over-the-counter for those ages 18 and older. This approval was based upon the sponsor's submission of a proposed educational program (Convenient Access Responsible Education Program, CARE℠ with the following elements: (1) labeling, packaging, Website, and informational 24-hour toll-free number, (2) education initiatives for healthcare providers, pharmacists, and consumers, (3) distribution plans, and (4) monitoring efforts to assess whether the Rx/OTC age distinction is understood and adhered to. We concluded that the CARE℠ προγραμ ισ σθφφιψιεντλυ ριγοροθσ το πρεωεντ υοθνγ ςομεν φρομ οβταινινγ Πλαν B® over-the-counter without the supervision of a practitioner licensed by law to prescribe the drug. We believe that the limitations described in the CARE program are commensurate with the specific concerns presented by Plan B, and are no more rigorous or burdensome than have been proposed by other sponsors for other drugs approved by FDA with restricted distribution.

Question 3. I am very concerned by the Union of Concerned Scientists survey of FDA scientists. About 150 FDA scientists said their superiors asked them to inappropriately exclude or alter technical information or their conclusions. About 170 FDA scientists said FDA decisionmakers asked them to provide incomplete, inaccurate, or misleading information to the public, industry, the press, or government officials. About 360 scientists don't believe they can express concerns about public health even within the Agency without fear of retaliation.

You spoke at the hearing about your commitment to make decisions based on science. Please describe the specific steps you would take, if confirmed as Commissioner, to see that scientific judgments at FDA are not clouded by politics. Do you have a plan to ensure that FDA leadership and management value and respect Agency scientists, and will not suppress their views? What will you do to identify and reprimand managers who compel certain answers or suppress scientific dissent?

Answer 3. I am committed to ensuring FDA makes decisions based on sound science and will make myself personally available to staff who want to appeal decisions made by FDA management. I believe that the need to appeal to me will be rare, however, because I will ensure that there are strong policies and procedures in place for resolving issues involving dissenting opinions. Efforts toward that end will include promulgating new policies and procedures as necessary, and strengthening, by process improvement and best practices measures, many of those that are already in place.

For example, we are working to ensure a rigorous ombudsman program through which staff are welcome to promulgate dissenting opinions. Staff may also invoke standard written procedures for facilitating and resolving differing professional opinions. In addition, Under the Secretary's leadership, FDA established a Drug Safety Oversight Board whose charter includes responsibility for deliberating on any dissenting opinions raised during evaluation of drug applications and surveillance of marketed products. Through these and other traditional management techniques, I believe we will successfully address any dissenting opinions, and I am committed to evaluating our processes and refining them as necessary to ensure that there is a healthy, open, unsuppressed scientific debate of issues at FDA.

Question 4. Representative Henry Waxman issued a report in June about the 50 percent decline in the number of enforcement actions since 2000. In one example, Agency headquarters declined to bring a criminal prosecution when the error of a medical gas company killed 4 nursing home patients in Ohio, and injured 6 others. In another example, FDA headquarters rejected taking action when errors by a blood bank resulted in 1 death and other patients receiving the wrong products.

Have you reviewed Mr. Waxman's report yourself? Do you believe the decline in enforcement actions is defensible? What is your reaction to each of the examples cited above? Can you assure this committee and the American public that you will vigorously enforce FDA's laws and regulations?

Answer 4. I have reviewed Mr. Waxman's report with serious concern, but I believe FDA enforcement cannot be properly judged merely by counting the number of actions taken by the Agency. Because FDA has increasingly used an enforcement strategy based on efficient risk management principles that focuses on combating the greatest public health risks and maximizing deterrent effect against potential violators, FDA's focus is on those firms and those violations that present the highest risk to consumers and public health. The Agency has taken prompt, targeted and aggressive action against firms that are in violation of law; thus the number may

have decreased, but the impact factor has increased, with positive deterrent effects on industry.

Notably, over the past few years FDA has won a string of legal actions against firms in violation of the law. These include settlements and penalties against a broad spectrum of violators. Criminal fines and equitable monetary payments including restitution and disgorgement resulting from FDA's enforcement actions alone since fiscal year 2000 have amounted to more than $2.5 billion—a figure that exceeds the Agency's annual budget. Recent years have also seen record individual FDA enforcement actions, including a case against a major pharmaceutical company in 2002 that resulted in a $500 million civil fine, the largest in agency history. In 2005, FDA enforcement efforts against another pharmaceutical company resulted in the largest seizure in FDA history—a seizure of nearly $600 million worth of goods.

The deterrent effect of these and other targeted actions can be seen in a number of ways including a small but steady decline since fiscal year 2000 in the rate of serious violations encountered in FDA inspections of regulated firms. The Agency is constantly working to improve its enforcement efforts by improving its management of enforcement activities and by bringing state-of-the-art science and risk-based management principles to our enforcement work.

Please allow me to address the specific incidents referenced in your question. In the medical gas case, FDA did not expend its enforcement resources on exacting punishment, but instead focused on trying to prevent further medical gas mix-up tragedies. FDA undertook a number of creative and meaningful steps including issuance of a guidance document, information sheet, and educational video for hospitals and other health care facilities on how to prevent medical gas mix-ups, creation of a widely-circulated poster (with the slogan, "if it won't connect, don't connect") combating a common cause of medical gas mix-ups, and work with industry to set standards for medical gas fittings that make it significantly more difficult for someone to accidentally connect the wrong medical gas to a gas supply system. In other words, although it did not pursue this particular single prosecution, FDA did proactively launch a number of measures that have resulted in a very positive public health outcome: since the Ohio incident to which you refer, there have been no more deaths from mix-ups of large cryogenic containers of medical gases.

In the blood bank incident, it is important to note that the Centers for Medicare and Medicaid Services (CMS) and FDA regularly collaborate when there are blood-related fatalities. This occurred in the referenced incident, where problems were identified on both the manufacturing and transfusion ends of the process. In this case, CMS did an inspection and took action against both the manufacturing and transfusion operations by limiting CLIA accreditation and suspending Medicare participation until corrections were made. In addition, a $10,000 Civil Money Penalty was imposed for errors that led to the fatality and $3,050 was imposed for two errors, one in 2001 and one in early 2004, that resulted in the wrong units being transfused without adverse health consequences. Here, when FDA considered issuing a warning letter, the establishment had already implemented corrective action that would have been sought in such a letter. You should note that prior to the incident to which you refer, the facility had been subject to routine inspections by FDA.

Finally, in reference to the last part of your question, I welcome this opportunity to assure the committee and the American people that I will vigorously enforce FDA's laws and regulations. As I stated in my prepared testimony to the committee, I cherish the trust of patients and the public and want to convey that I am committed to using FDA's laws and regulations to make sure that each action, decision or activity taken by the Agency is directed to preserving their lives and protecting their health.

Question 5. As you know, Chairman Enzi and I are working on a drug safety bill, and of course there are a number of important reauthorizations for us to complete next year, including the drug and device user fee programs and the pediatric drug provisions. Are you committed to working with this committee to get these bills done and implemented promptly and appropriately?

Answer 5. I am committed to working closely with Congress to reauthorize these critically important programs.

Question 6. I am very concerned about the effect of the tight budget on the FDA. This year's budget directed funds away from important programs, especially in the food center. I fear it will only be worse next year.

At the same time, FDA's product review programs are relying increasingly on user fees because appropriations have not kept pace with FDA's needs. I think appro-

priated funds are the first choice to fund the Agency, yet to address a real and critical funding shortfall, it seems FDA must turn increasingly to user fees.

As Commissioner, what will you yourself do to assure that FDA's appropriations are sufficient to meet its needs and accomplish its public health goals? What will you do specifically at each level, at the Department, at OMB, and at Congress? If cuts in appropriations are made, how will you meet the Agency's public health goals in each product area: foods and dietary supplements, drugs, biologics, medical devices, electronic products?

Answer 6. When I was appointed Acting Commissioner in September 2005, one of my first priorities was to develop a fiscal year 2007 budget proposal for FDA that meets the Agency's needs and advance the proposed budget through the Administration and congressional approval processes. These efforts resulted in proposed increases in the President's fiscal year 2007 budget to address a number of high priority public health concerns. The proposed increases include pandemic preparedness, food defense, critical path, drug safety, tissue safety, funding to meet user fee triggers, pay increases for cost of living, and increases to support our essential infrastructure needs. In the months since the President released the fiscal year 2007 budget, I have been working personally and directly with the members of the House and Senate Appropriations Committees and others in Congress to secure these important funding increases.

Question 7. 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/english/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? If so, please explain how the Agency intends to communicate these recommendations to both dentists and patients.

Answer 7. In our 2002 proposed reclassification of dental amalgam, the Agency recommended that dental amalgam devices have ingredient labeling. This same document also discusses appropriate handling of dental amalgam. FDA has looked at the literature on the potential toxicity of dental amalgam systematically over the years along with our colleagues from the Centers for Disease Control and National Institute for Dental and Craniofacial Research. All of our reviews have indicated that FDA's position on labeling is supported in the literature. That is, no warnings are recommended on amalgam devices against use in pregnant women or children. FDA continues to regularly review any new data on these topics that might alter our view.

Question 8. When clearing or approving a device, FDA must consider risks vs. benefits. Please discuss the risks of dental amalgam, which contains mercury, as compared to its benefits, especially considering the availability of cavity-filling alternatives, such as resin.

Answer 8. Dentists today have numerous materials from which to select when restoring teeth, including amalgam, composite (resin), glass ionomer cement, gold foil, cast metals, ceramics, and metalceramics. Specific clinical situations, however, dictate a much narrower range of appropriate restoration options.

The clinical decision as to which restorative material to place is complex, involving factors relating to the tooth, the patient, the clinician, and the properties of the restorative materials. Individual restorative materials ideally are applied in a defined set of clinical circumstances, and it is not possible to freely substitute one material for another and expect long-term success.

For much of the last century it was believed that dental caries could be treated away with restorations (Anusavice, 1989). Clearly, this is not the case. The long-term consequences of the insertion of the first restoration in any tooth always must

be a consideration in the treatment decision (Lutz et al., 1987). Dental restorations have a limited clinical durability. As restorations need replacement, an increasing amount of tooth structure is lost and the patient may enter into a repetitive restorative cycle with larger restorations, weaker teeth, and more complex therapy (Elderton and Davies, 1984). Indeed, it has been estimated that as many as two-thirds of restorations placed each year are replacements for existing restorations (Maryniuk and Kaplan, 1986). As the cavity size expands, the range of restorative materials to effectively employ becomes limited, and the option of appropriately placing a more economical direct restorative material that conserves tooth structure is lost.

There are potential risks and benefits from any restorative material. For dental amalgam:

POTENTIAL RISKS

- Exposure to minute amounts of elemental mercury
- A small proportion of individuals may manifest allergic reactions to amalgam.

BENEFITS

- Dental amalgam is durable.
- It is least technique sensitive of all restorative materials.
- It is applicable to a broad range of clinical situations.
- It is long lasting.
- It often can be repaired.
- Many restorations are replacements. Most of these will require amalgam or other metallic materials, because composite materials often lack sufficient strength or durability to be considered adequate substitutes.

Question 9. I understand dental amalgam is the largest source of mercury in wastewater and, in some communities, the largest source of mercury in the air (due to cremation). Please discuss the Agency's obligations under the National Environmental Policy Act, section 746 of the Federal Food, Drug, and Cosmetic Act, and the Agency's implementing regulations to consider the environmental impact of the use of dental amalgam.

Answer 9. As with other FDA classification regulations, the Agency included an environmental impact section in the classification rule. This section noted that FDA had determined under 21 CFR 25.34(b) that its classification of the devices is of a type of action that does not individually or cumulatively have a significant effect on the environment and therefore, under the National Environmental Policy Act, neither an environmental assessment nor an environmental impact statement was required. FDA is evaluating all comments on the proposed rule and in this context will consider the treatment of this issue under NEPA.

Question 10. I understand that the FDA clears dental amalgam capsule using a pre-market notification under section 510(k) of the Federal Food, Drug, and Cosmetic Act, as "substantially equivalent" to a non-mercury powder alloy. Please explain the Agency's determination that dental amalgam capsule is substantially equivalent to a non-mercury powder alloy. In particular, it would seem that dental amalgam would "raise different questions of safety and effectiveness" than a non-mercury product.

Answer 10. All three dental amalgam devices (dental mercury, amalgam alloy and encapsulated amalgam) are pre-amendments devices, i.e., they were legally on the market prior to enactment of the 1976 Medical Device Amendments. Similar products to be marketed for the first time after 1976 require the submission of a pre-market notification (510(k)) and a substantial equivalence determination to these three pre-amendments devices (containing mercury) before they can be marketed. Dental mercury (class I) and amalgam alloy (class II) when sold separately are intended to be mixed together to form the dental amalgam device. Encapsulated amalgam is a device that contains dental mercury and amalgam alloy separated via a septum in the capsule. It is therefore a combination of the class I and class II devices. When two regulated devices are sold together they are generally regulated at the higher class, in this case, class II. We have not cleared the dental amalgam devices as substantially equivalent to non-mercury powder alloy.

Question 11. I understand that FDA is holding an advisory committee meeting in September on the neuro-toxicity of dental amalgam. I believe such a meeting would be required to be "balanced," yet there are allegations that FDA has chosen as members only those who favor FDA policies on dental amalgam. Please explain.

Answer 11. The assembled advisory panel consists of CDRH's Dental Products Panel and CDER's Peripheral and Central Nervous System Drugs Advisory Committee. The combined expertise of these two panels will facilitate and enhance a discussion of the peer reviewed literature on dental amalgam and any adverse health effects. We believe that the panel consists of scientists who clearly will be able to discuss with intellectual honesty the material presented to them from the literature. We feel that the expansion of the panels' expertise to include neurologists and toxicologists will only benefit and balance this process.

Question 12. 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? Currently, FDA requests that industry voluntarily submit information on such products, but it has not required companies to do so. Moreover, it appears that FDA would have to start from scratch having no information and be required to prove that such a product was unsafe if a company refused to comply voluntarily. Why is a voluntary system sufficient to protect the public health and address the environmental concerns?

Answer 12. We believe that our current system is the appropriate approach to the oversight of bioengineered foods. As noted in a 2004 report on genetically-engineered foods from the National Academy of Sciences (*Safety of Genetically Engineered Foods Approaches to Assessing Unintended Health Effects*), a policy to assess products based exclusively on their method of development is scientifically unjustified. We believe our current authority under the Federal Food, Drug, and Cosmetic Act (the act) is sufficient to oversee the safety of bioengineered foods. Under the act, we have authority to require pre-market review and approval of a substance introduced into food unless its use is generally recognized as safe (GRAS). We also have broad authority to take action against a food if it bears or contains any poisonous or deleterious substance that may render it injurious to health, such as increased levels of a naturally-occurring toxicant. Our consultation process provides us and developers of bioengineered crops with a tool to ensure that safety questions are resolved prior to marketing. We believe that our post-market legal authorities, in tandem with market and trade forces, provide significant incentives for developers of bioengineered crops to consult with FDA.

We believe that bioengineered foods intended for commercialization in the United States have been the subject of a consultation prior to marketing. Our current approach is working well, and we do not believe that there is need or scientific justification for a pre-market approval program specific to bioengineered foods.

Question 13. 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, 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 13. FDA continues to meet internally and to work with other Federal Agencies to determine the most appropriate system for regulation of genetically engineered animals. At the same time, industry has submitted, and the Agency is reviewing, applications for genetic constructs inserted into transgenic animals to be approved as new animal drugs. None of these applications have received FDA approval yet.

Question 14. 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 14. I agree that there is compelling evidence of a public health concern associated with consumption of partially hydrogenated vegetable oils (*trans* fats), and FDA is taking steps to foster the development of healthier food products that are lower in *trans* fats.

Most significantly, as you are aware, the FDA's *trans* fat labeling rule became effective just this past January. This rule requires the amount of *trans* fat in grams to be declared on the Nutrition Facts panel of all foods under FDA jurisdiction. The rule does not apply to foods served in restaurants unless a claim is made, in which case certain nutrition information must be provided. We believe that this action will have a significant positive impact in reducing the levels of *trans* fats in packaged foods and in preventing coronary heart disease and death. We will be closely monitoring the effectiveness of this rule.

FDA has also updated its Website and undertaken other educational and outreach efforts to increase consumer understanding of the Nutrition Facts panel and to in-

form consumers of how to use the label to choose products low in *trans* fat, saturated fat, and cholesterol.

Finally, FDA has received a citizen petition requesting that FDA undertake several other regulatory actions and educational activities to further limit the use of *trans* fats in processed foods and to encourage manufacturers and restaurants to switch to more healthful oils. The Agency is currently reviewing this petition.

Question 15. How do you intend to implement the 2004 recommendations of the Institute of Medicine with respect to sugars and added sugars in foods?

Answer 15. The Nutrition Facts panel (NFP) of food labels provides consumers with information on total carbohydrates and total sugars in a product. The ingredient list provides consumers with information on what is in the product, including ingredients that are sources of added sugars. The Agency intends to issue an Advance Notice of Proposed Rulemaking (ANPRM) on updating the NFP based on several reports issued by the Institute of Medicine (IOM). Included in this ANPRM are questions regarding how information on carbohydrates should be presented in the NFP.

Question 16. 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. The FDA's own research demonstrates that consumers are misled by them. The claim for green tea is particularly dubious:

> One weak and limited study does not show that drinking green tea reduces the risk of prostate cancer, but another weak and limited study suggests that drinking green tea may reduce this risk. Based on these studies, FDA concludes that it is highly unlikely that green tea reduces the risk of prostate cancer."

Answer 16. Although the Federal Food, Drug, and Cosmetic Act directs FDA to authorize only health claims supported by "significant scientific agreement" to appear in the labeling of conventional foods, the U.S. Court of Appeals for the DC. Circuit held unambiguously in *Pearson* v. *Shalala* and *Whitaker* v. *Thompson* that the First Amendment does not permit FDA to prohibit health claims that the Agency determines to be potentially misleading unless the Agency also reasonably determines that a disclaimer would not eliminate the potential deception. FDA would risk judicial sanctions if it were to ignore the DC. Circuit's rulings or subsequent rulings by lower courts directing FDA to permit certain qualified health claims. Further, although FDA's consumer research raises significant concerns about consumer understanding of some disclaimers used in current qualified health claims, the Agency's research is ongoing, and at this point, we feel it would be imprudent to change current policy based on incomplete data.

The FDA has progressed through a series of steps to implement the *Pearson* and *Whitaker* decisions. In December 2002, the FDA announced a major new initiative, the "Consumer Health Information for Better Nutrition Initiative." As part of the Initiative, FDA conducted consumer studies on ways to communicate different levels of scientific support for claims about the relationship between a food substance and reduced risk of a disease. FDA is continuing to conduct consumer study research for appropriate qualifying language for health claims such that consumers are not misled.

Question 17. During your tenure at the National Cancer Institute, you may have worked in close collaboration with companies from the pharmaceutical, biotechnology, or medical device industries. Could you please identify any matters from which you are recused because of such collaborations?

Answer 17. In order to assure the fruits of biomedical research would be translated into life saving and health enhancing interventions for patients and the public, I have focused my efforts on a comprehensive strategy, from discovery to development to delivery. This continuum spans the academic, private, and public sectors, and requires cooperation and at times close collaboration among them. I have always respected and maintained the legal and ethical boundaries of these delicate relationships. My work at NCI did not create any interests that would constitute a real or apparent conflict of interest under the government ethics rules. I will seek and abide by the advice of agency ethics counsel in the Office of the General Counsel with respect to any potential conflict of interest or recusal.

Question 18. The FDA recently announced that it will be redrawing its guidelines for staffing outside advisory committees, to make greater efforts to exclude scientists with conflicts of interest who currently get waivers to serve on these committees, and to make the process more open to outside participation, with increased transparency. Could you please give us the specifics in each of these areas: Which con-

flicts of interest will be eligible for waivers? Will any conflicts be grounds for automatic exclusion under the new guidelines? How will the Agency encourage greater public participation in the staffing of these committees? How will its waiver and recusal decisions become more transparent?

Answer 18. In a speech given July 24, 2006, Deputy Commissioner Dr. Gottlieb discussed efforts to revise guidelines detailing the kind of industry ties that are permitted for those who serve on our advisory committees (see *http://www.fda.gov/oc/speeches/2006/conference0724.html*). More specifically, we plan to revise the guidance documents used to determine how potential conflicts are evaluated, how waivers are granted, and how information regarding conflicts and waivers is disclosed. The goal is to make the process more transparent and clarify more of the case-by-case qualitative judgments we make when we evaluate each potential conflict. We do not plan to re-write existing rules, but instead to provide additional guidance and clarity regarding implementation of the existing statutory and regulatory framework regarding conflicts of interest. The revision process is currently underway and is a high FDA priority. We will make public the revised guidances as soon as they are completed.

We believe that these administrative changes will substantially improve the transparency of the process of managing our advisory committees, evaluating potential conflicts, and granting waivers where appropriate.

Question 19. The public should be given a real opportunity to nominate members of its advisory committees. How do you intend to make that happen?

Answer 19. Our process has always welcomed nominations for our advisory committees from any interested party. FDA generally notifies the public about vacancies on committees through *Federal Register* notices on an annual basis. Many professional societies use these notices to share news of potential vacancies among interested professionals. We are committed to welcoming and carefully reviewing nominations that we receive from the public for advisory committees.

Question 20. Consumers need to rely on food labeling to make healthy choices and decrease the risk of obesity. Yet reports from consumer groups and State officials indicate there are numerous examples of mislabeled products, and the FDA has brought an insufficient number of enforcement actions to address the problem. Why doesn't FDA take action when competitors and consumer groups bring misbranded products to its attention? If FDA lacks sufficient funding to do its job, what will you do to get it the resources it needs?

Answer 20. As part of FDA's Nutrition Labeling and Education Act (NLEA) Compliance Program (the Compliance Program), FDA investigators routinely review selected food labels during regularly scheduled food manufacturer inspections performed under the Agency's food safety compliance programs. The Compliance Program includes guidance for FDA investigators to review labels and collect samples for nutrition analysis of domestic and imported food products.

Between October 1, 2004, and December 6, 2005, FDA conducted approximately 28,000 field examinations of domestic and imported food labels. FDA also collected 543 samples for nutrient analysis and/or label review. As a result of FDA's label reviews and nutrient analysis, FDA issued 56 Warning Letters addressing misbranding violations involving a variety of food products.

FDA is updating the Compliance Program to provide increased emphasis on ingredient labeling in conjunction with our efforts to implement the Food Allergen Labeling and Consumer Protection Act, which became effective on January 1, 2006.

Question 21. I would like you to comment further about salt.

In a 2004 Commentary in The American Journal of Public Health, Claude Lenfant, then director of the National Heart, Lung, and Blood Institute, and two colleagues noted that diets high in salt, or sodium, increase blood pressure and increase the risk of heart attacks and strokes. They estimated that halving the sodium content of the American diet could save 150,000 lives per year. The January 2005 Dietary Guidelines for Americans, the Institute of Medicine of the National Academy of Sciences, the World Health Organization, the American Medical Association, and other authoritative health agencies have called for reducing sodium levels in the American diet. A 1979 advisory committee report to the FDA concluded that salt could not be considered "generally recognized as safe" and recommended that the FDA limit the salt content of packaged foods.

How many FTEs has the FDA devoted over the past 10 years to this enormous public health problem? As Commissioner, what will you do to lower salt levels in packaged foods, restaurant food, and the American diet generally?

Answer 21. I believe this is an important issue for public health and that FDA has a central role to play in efforts to lower salt levels in the American diet. I will

continue to work with FDA's Center for Food Safety and Applied Nutrition (CFSAN) on this issue, emphasizing the need for effective, feasible measures that will reduce salt consumption.

Our current reporting system does not allow us to distinguish the FTEs devoted specifically to salt over the past 10 years; however, we are presently working diligently on issues related to reducing salt in the American diet. I believe you are aware that FDA received a citizen petition in late 2005 that proposed, among other things, to require reductions in the salt content of processed foods, including processed foods intended for restaurant use. In preparation for an informed and comprehensive response to this citizen petition, FDA is planning as a first step to announce the availability of the citizen petition for comment in an upcoming Federal Register notice. This announcement will likely be followed by a public meeting intended to solicit comments from stakeholders and the public in general. FDA feels this additional information is important given the complexity of the regulatory response proposed in the citizen petition and the complexity of issues surrounding the use of salt in foods in general.

I should also note that FDA has been active in its efforts to reduce salt in foods through providing information for consumers. For example, FDA requires disclosure of the sodium content on food packaging, has an authorized health claim relating to reductions in the risk of high blood pressure for foods low in sodium, and has qualifying levels of sodium that a food may contain for foods to be labeled "healthy."

Question 22a. In 2002, Congress gave the FDA new authorities to protect the Nation's food supply against the threat of intentional contamination and other food safety emergencies.

However, due to inadequate staffing, FDA has turned much of its border inspection responsibilities over to Customs and Border Protection (CBP). FDA also lacks mandatory authority to recall contaminated food that it regulates.

How many ports of entry are used for FDA inspected products?

Answer 22a. According to U.S. Customs and Border Protection (CBP), there are 317 official ports of entry in the United States (U.S.). FDA staff provides coverage on a routine basis at the 90 ports of entry through which the greatest volume of FDA-regulated products pass. These ports include all major sea/air ports and the highest volume land border ports.

Question 22b. How many FDA inspectors check ports of entry?

Answer 22b. FDA staff provides coverage on a routine basis at the 90 ports of entry through which the greatest volume of FDA regulated products passed. In fiscal year 2005, 424 ORA employees conducted Field Exams on imported, FDA-regulated commodities offered for entry into the United States.

Question 22c. How many ports of entry are now covered by CBP employees instead of trained FDA inspectors?

Answer 22c. First, it is important to note that FDA has not turned much of its border inspection responsibilities over to Customs and Border Protection (CBP), as you suggest. Staff from FDA's Office of Regulatory Affairs (ORA) currently provides coverage at the 90 ports of entry. FDA has not requested CBP to provide coverage at any ports of entry *in lieu* of FDA coverage at those same ports of entry. FDA's import data system, Operational and Administrative System for Import Support (OASIS), receives electronic data from CBP's Automated Commercial System for FDA-regulated merchandise entered through all 317 ports of entry. If, upon review of this data, FDA decides to sample or examine product, FDA and CBP regulations require that the product be held under bond until sampled/examined and released by FDA. Pursuant to the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (BT Act), FDA and CBP signed a Memorandum of Understanding (MOU) that has allowed ORA to commission approximately 9,500 CBP Officers in ports and other remote locations to conduct, on FDA's behalf, investigations and examinations of imported foods at ports where FDA may not currently have staff or to augment FDA staff at ports that do have an FDA presence. FDA has not yet had a need to utilize this MOU.

Question 22d. What sort of food safety training do these CBP inspectors have?

Answer 22d. FDA senior import personnel provided training to selected CBP officers following the enactment of the BT Act. The CBP officers were trained in how to conduct food import field examinations. They were also taught how to sample, package and ship products to FDA laboratories for analysis. Upon return to their respective ports, it was the responsibility of these selected CBP officers to train other commissioned officers (CBP) within their port's jurisdiction via the "train the trainer" model. Additional guidance for commissioned CBP officers, should there be

an occasion where they would have to act on FDA's behalf, would come via mission specific assignments from FDA's Prior Notice Center.

Question 22e. Do you think the FDA needs mandatory recall authority, such as it has for infant formula and medical devices, to quickly remove contaminated food from the market?

Answer 22e. FDA, through its authority under the Federal Food, Drug, and Cosmetic Act, can remove a violative product from the market by using its seizure authority. It is also important to note that the BT Act granted substantial new powers to FDA to administratively detain foods for which there is credible evidence or information that the food presents a serious adverse health consequence or death to humans or animals. This authority is coupled with additional authority, under certain circumstances, to detain imported foods at ports of entry for a period of time sufficient to enable their inspection. Since enactment of this important legislation, FDA has been busy implementing these and other authorities provided under the BT Act.

Question 23a. Increasingly, imported foods are the source of food-borne illness. For example, in 2003 a hepatitis A outbreak associated with green onions imported from Mexico sickened over 550 people. Since 1994 the volume of food imports regulated by the Agency has grown fivefold. Meanwhile FDA inspects fewer than 2 percent of these shipments with an increasingly diminishing budget.

With dwindling resources how would you improve FDA's oversight of imported food?

Answer 23a. To manage the increasing volume of imported food shipments, FDA is using risk management criteria to achieve the greatest protection possible when it comes to safeguarding imported food. Currently, a significant effort is underway to broaden, develop and apply appropriate knowledge-based risks to the examination of imported food.

In addition, the Bioterrorism Act [BT Act] provided a significant new tool that enhances FDA's ability to electronically review FDA-regulated imported shipments. As you know, that law requires that FDA receive prior notification before food is imported or offered for import into the United States. Advance notice of imported food shipments, called "Prior Notice," allows FDA, with the support of the CBP, to target food import inspections more effectively and to help protect the Nation's food supply against terrorist acts and other public health emergencies. With the Prior Notice requirement, specific information mandated by the BT Act must be submitted to FDA before the imported food arrives in the United States. This allows the electronic system to review and screen the shipments for potential serious threats to health (intentional, alleged or otherwise) before the food arrives. It also allows FDA staff to review Prior Notice submissions for those products flagged by the systems as presenting the most significant risk. FDA worked very closely with CBP in developing the targeting criteria. FDA's experience with the prior notice system has been that it permits FDA to further refine our risk-based targeting criteria and allows us to allocate resources for inspections more effectively.

The fiscal year 2007 President's budget request includes almost $20 million in increases for food defense efforts, including $3.2 million to support the Field's risk-based domestic and imports food safety operations. The request supports continuing efforts to target potentially high-risk imported foods through Prior Notice Import Security Reviews, which utilize information from intelligence data, records of FDA inspections, Prior Notice submissions, and other sources. Also included in the request is $12.7 million for the Food Emergency Response Network, $1.5 million for Crisis Management, and $2.5 million for Bio-surveillance activities.

Question 23b. What percentage of food shipments should FDA be inspecting and on what basis do you make that determination?

Answer 23b. In fiscal year 2005, nearly 8.7 million line entries of imported food were offered for entry into the United States, on which FDA conducted approximately 85,000 food import field examinations (exams). FDA believes that the best approach to improving the safety and security of imported food is to devote resources to expanding and refining the targeting criteria and to conduct more intensive reviews on potentially high risk entries, rather than to simply increase the percentage of food import lines that receive a field exam. A food import field exam is a visual and physical examination of a food product to determine whether it complies with FDA requirements for admissibility. During food import field exams, FDA personnel check attributes such as damage during storage or transit, inadequate refrigeration, rodent or insect activity, presence of lead in dinnerware, appearance of decomposition, and compliance with labeling requirements. Food import field exams have always been just one part of FDA's import strategy. FDA does not rely solely

on the physical examination of a product through a food import field exam to reduce the potential risks posed by imported foods.

While we do not physically inspect every shipment, it is important to note that every shipment containing FDA-regulated products entered through CBP's automated system is electronically reviewed by FDA's system. FDA's import data system, 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 method allows FDA to concentrate its enforcement resources on high-risk shipments while allowing low-risk shipments to proceed.

In addition, FDA receives and its data systems review approximately 35,000 Prior Notice submissions containing specific information about incoming food shipments every day.

Question 24. In August 1977 the FDA published a proposed rule to withdraw approval of the subtherapeutic use of penicillin in livestock. Almost 30 years later, in May 2004, the Director of the Center for Veterinary Medicine wrote to the three manufacturers of penicillin for animal use—Alphamra, Pennfield Oil, and Phibro Animal Health—to remind them that the 1977 proposal is still pending and to express its concerns about their products' "possible role in the emergence and dissemination of antimicrobial resistance." So far as I know, the companies have not responded.

Please explain what steps you will take as Commissioner to complete the work on this 1977 proposal. Do you believe the FDA needs additional legal authority to complete what the FDA proposed in August 1977, and to address antibiotic resistance more generally?

Answer 24. FDA's Center for Veterinary Medicine (CVM) has a working group tasked with reviewing the scientific basis for the 1977 Notice of Opportunity for a Hearing (NOOH) for penicillin products and, in light of the review of the penicillin new animal drug applications (NADAs), to make a recommendation regarding actions that may need to be taken. The group has completed its review of NADAs providing for the use of penicillin for nontherapeutic uses and is currently finalizing its recommendations regarding the safety of these penicillin products. CVM intends to solicit public input once the working group has completed its work.

Using its existing legal authorities, FDA has developed a regulatory strategy for managing the potential risks associated with the use of antimicrobial drugs in food-producing animals. This innovative approach includes the use of risk assessment to quantify the human health impact from antimicrobial use in animals, in conjunction with robust monitoring through the National Antimicrobial Resistance Monitoring System (NARMS), research, and risk management. FDA does not believe that any additional legal authority is required, but the Agency will continue to work with Congress and various stakeholders to address safe use of antimicrobials in food animals and ensure that significant human antimicrobial therapies are not compromised or lost.

Question 25. It has been nearly 2 years since the manufacturer of one of the progestin-only oral contraceptives informed me that FDA was discussing with it a change to the drug's labeling to indicate that some women experience reductions in breast milk production when on the progestin-only pill.

This matter was brought to my attention by a constituent, who experienced this problem when nursing each of her first two children. Her first child did not thrive before she discovered the problem, and she had to switch him to formula because she had stopped producing milk. His lack of weight gain fortunately reversed once he was on formula. She noticed this problem more quickly with her second child, stopped using the pill, and was able to continue nursing the child.

The drug is currently promoted, and so I assume labeled, as having no negative side effects on breast feeding. Although I understand that clinical trials of the drug showed this to be the case for the women in the trials, these trials did not include that many women, and they clearly do not rule out the possibility that some women do experience negative side effects on breast feeding.

I believe that reduction in breast milk production in a nursing mother is a serious, if rare, side effect of these drugs that nursing mothers should be warned about. Do you agree? If you do not agree, please explain. If you do agree, please explain why it has taken so long to address this serious problem and when you anticipate that the drug's labeling will properly warn women about this drug risk.

Answer 25. We agree that a statement concerning the risk of a reduction in breast milk production should be included in labeling of progestin-only nonemergency oral contraceptive products. Accordingly, we are in the process of ensuring that the labeling for progestin-only nonemergency oral contraceptives is revised to indicate that

there have been rare post-marketing safety reports of decreased milk production in lactating women. To this end, the following statement (underlined text) has been added to the labeling for Nor-QD (norethindrone 0.35 mg tablets), a progestin-only oral contraceptive, under the section PRECAUTIONS, Nursing Mothers.

> "No adverse effects have been found on breastfeeding performance or on the health, growth, or development of the infant. However, isolated post-marketing cases of decreased milk production have been reported. Small amounts of progestin pass into the breast milk, resulting in steroid levels in infant plasma of 1–6 percent of the levels of maternal plasma."

We are in the process of ensuring that similar language is included in the approved labeling for other progestin-only non-emergency oral contraceptives.

Question 26. Earlier this year, the FDA issued a final rule to improve how prescription drugs are labeled. In the preamble of that final rule, the Agency made the extraordinary and unprecedented claim that its regulation of prescription drugs preempted many different kinds of State product liability claims against the manufacturers of prescription drugs. The Agency made this statement despite the fact that it had said in the preamble to the proposed regulation that it did not intend the regulation to have preemptive effect and despite a statement in the 1962 drug amendments that Congress only rarely intended FDA's regulation of prescription drugs to preempt any State law, let alone product liability actions. Moreover, the Agency did so by completely overstating and mischaracterizing the Agency's authority over drugs postapproval. Do you agree with this claim, and if so, why?

Answer 26. I do agree with the statements FDA made in the preamble to the final rule on prescription drug labeling with regard to preemption. I do not agree that FDA overstated and mischaracterized the Agency's authority over approved drugs, nor that the Agency made any extraordinary or unprecedented claims.

By way of explanation, FDA issued a proposed Physician Labeling Rule in 2000. FDA received numerous comments in response to the proposal regarding the product liability implications of revising the drug labeling, in particular regarding the truncated description of the risks in the new highlights section. The Administrative Procedure Act requires the Agency, when issuing a final rule, to address the comments it receives in response to proposed rules. The discussion in the preamble to the final rule regarding Federal preemption that you are referring to was written in response to comments received, and merely restates the Agency's longstanding position as articulated in *amicus* briefs filed in court by DOJ in cases regarding Federal preemption and drug labeling. These product liability cases involved State law challenges to FDA approved labeling. DOJ argued on behalf of FDA that such law suits are preempted by the act when State requirements cause drug products to be misbranded under Federal law. The 2006 preamble merely set out well settled principles of preemption law and FDA's current understanding of the way in which a State tort judgment can interfere with FDA's implementation of Federal law.

In the context of drug labeling, Congress has authorized FDA to apply its scientific expertise to determine, in the first instance, what labeling, including warnings, are appropriate and necessary for a particular drug. See *Henley* v. *FDA*, 77 F.3d 616, 621 (2d Cir. 1996); *Public Citizen Health Research Group* v. *Commissioner*, 740 F.2d 21, 28 (D.C. Cir. 1984). Therefore, FDA's determinations about the scientific evidence surrounding a drug product, and determinations about whether particular labeling is false or misleading are paramount. In addition, even in the absence of an express preemption provision, implied conflict preemption principles still function to preempt State law. See *Geier* v. *American Honda Co.*, 529 US 861 (2000). This type of preemption arises when there is conflict between Federal and State law, and the preemptive effect can occur with any Federal regulation. Under the Supremacy Clause (U.S. Const. art. VI, cl.2), a State may not force a drug manufacturer to choose between compliance with Federal law and State law. See *Geier*, at 873. In addition, companies could be held liable under State product liability law where State requirements neither conflict with Federal requirements nor frustrate Federal purposes.

FDA's regulation of prescription drugs is designed to ensure each drug's optimal use through requiring scientifically substantiated warnings. Under the Federal Food, Drug & Cosmetic Act, FDA is the public health agency charged with ensuring that drugs and devices are safe and effective, and that the labeling of drugs and devices adequately inform users of the risks and benefits of the product. FDA employs scientists and other experts who review the information submitted by the manufacturer on a product's risks and carefully titrate the warnings, etc. that should be placed on the labeling. FDA continuously works to evaluate the latest available scientific information to monitor the safety of products and to incorporate information into the product's labeling when appropriate. The public health risks as-

sociated with overwarning are as great as—if not greater than—the health risks associated with underwarning. Overwarning can cause patients not to take beneficial drugs and doctors not to prescribe them.

Under-utilization of a drug based on dissemination of scientifically unsubstantiated warnings, so as to deprive patients of beneficial, possibly lifesaving treatment, could well frustrate the purposes of Federal regulation as much as over-utilization resulting from failure to disclose a drug's scientifically demonstrable adverse effects. Further, allowing unsubstantiated warnings may also diminish the impact of valid warnings by creating an unnecessary distraction and making even valid warnings less credible.

RESPONSE TO QUESTIONS OF SENATOR GREGG BY ANDREW C. VON ESCHENBACH

Question 1. As you know, earlier this month, the Senate passed Senator Vitter's drug importation amendment to the DHS appropriations bill. This amendment *prevents* Customs and Border Protection from using funds to stop the personal importation of FDA-approved drugs from Canada. I opposed this approach to dealing with the importation of prescription drugs.

Do you believe the Vitter amendment provides for safe importation of drugs? Should the Vitter amendment be included in the Homeland Security Appropriations Conference Report?

Answer 1. I agree with you that this is not the right approach to deal with the importation of prescription drugs. The Administration strongly opposes a provision to the Homeland Security Appropriations Bill allowing the personal importation of prescription drugs, and I agree. This provision would prevent the U.S. Customs and Border Protection (CBP) from assisting Food and Drug Administration (FDA) efforts to prevent the importation of misbranded and potentially unsafe drugs. It would also prevent CBP from helping FDA enforce section 801(d)(1) of the Federal Food, Drug, and Cosmetic Act (the act), which prohibits anyone other than the original manufacturer from importing into the United States a prescription drug that was originally manufactured in the United States and then sent abroad. Congress enacted section 801(d)(1) in 1987 to help safeguard the safety and integrity of the domestic drug supply.

The December 2004 HHS Task Force Report on Drug Importation identified significant safety risks associated with drugs imported by individuals. FDA has found that many drugs ordered at Websites from apparently Canadian pharmacies, in fact, originate from countries around the world. If this provision is enacted into law, FDA's resources would not be sufficient to examine these drugs at the border to ensure that they are FDA-approved and not counterfeit. The Administration recommends that the amendment be deleted because it could threaten the health and safety of Americans.

GENERIC DRUGS

Question 2. Not only has PDUFA ensured the timely review of new drug applications, but it now funds almost half of the Agency's drug review activities. It is this success that prompted me to co-author legislation that extended the user fee model to the FDA's review of medical devices and animal drugs. I understand that there is a backlog of about 200 generic drug Abbreviated New Drug Applications at the Office of Generic drugs and this backlog can be expected to grow given the relatively large number of blockbuster drugs that are coming off patent in the next few years.

Would a steady stream of income through a user fee program for generic drugs enable the Agency to increase their resources to reduce the backlog?

Answer 2. As you may know, the Prescription Drug User Fee Act does not apply to generic drugs approved under the ANDA process, section 505(j) of the Federal Food, Drug and Cosmetic Act. We have heard public discussion of a generic drug user fee program, but at this time, the Administration has no position on such proposals.

Question 3. Both FDA and the generic drug industry recognize that the citizen petition process has been used to cause delay to the introduction of generic drugs.

Do you believe the current structure is balanced? Does FDA need to act to ensure generic drugs are not delayed on their way to market?

Answer 3. FDA regulations permit any interested person to file a citizen petition requesting FDA "to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action" (Title 21, *Code of Federal Regulations* 10.25 and 10.30). Citizen petitions may be submitted at any time requesting that FDA impose new criteria for approval of ANDAs.

It is incumbent upon FDA to consider and address the merits of petitions. The data and information submitted with these petitions may require detailed analysis and precise scientific documentation, often involving multiple disciplines within CDER. Because the same issues sometimes are raised in a subsequent court challenge to an ANDA approval and because petitioners sometimes submit nonscientific petitions that raise purely legal questions related to ANDA approvals, a thorough legal review is also necessary. Although it is not required that a citizen petition response be issued before approval of a related ANDA, it is important that FDA comprehensively assess the scientific issues prior to approval of the ANDA. It is very rare that petitions present new issues that CDER has not fully considered, but the Agency must nevertheless assure itself of that fact by reviewing the citizen petitions.

CDER has made considerable efforts in the last year-and-a-half to improve the process for responding to citizen petitions. As part of this process, OGD constituted a group of highly qualified and skilled scientists dedicated to assessing the citizen petitions related to generic drugs and formulating FDA's responses to them. Other improvements include: increased prospective management of the petition response process; development of clear timelines for completing actions; and improved communication among the CDER components involved in responding to citizen petitions.

BIOSHIELD

Question 4. There appears to be some differences of approach by CBER and CDER regarding the pathway to licensure for biodefense countermeasures. CBER appears to put more weight on the risk of a terrorist event and the need to ensure safety and efficacy while CDER appears to discount the risk of a bio-terrorist attack to a greater degree in ensuring safety and efficacy.

How would you attempt to reconcile these apparent inconsistencies between the centers?

Answer 4. FDA remains strongly committed to facilitating the development and availability of safe and effective medical countermeasures to protect the public against a broad range of terrorist threat agents. To this end, our Medical Centers (CBER, CDER, and CDRH) are working closely with sponsors who are interested in developing new products to diagnose, treat, and prevent illnesses caused by chemical, biological, radiological, and nuclear (CBRN) agents.

The legal standards for product approval, clearance, and licensure under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act apply equally to countermeasures and to other products. Similarly, the legal standard for issuance of an Emergency Use Authorization (EUA) applies to all types of countermeasures. These legal requirements establish the framework for our scientific review of product submissions.

As we develop new counterterrorism policies, we look for opportunities for a comprehensive (cross-Center) approach. For example, the Animal Efficacy Rule (Animal Rule) was jointly promulgated by CBER and CDER to help expedite the regulatory pathway for new countermeasures. Under the Animal Rule, animal efficacy data may be used when efficacy studies in humans are not ethical and field trials are not feasible. More recently, FDA published a Draft Guidance on Emergency Use Authorization of Medical Products (Draft Guidance). The Draft Guidance was developed by an agency-wide working group and presents Agency recommendations on EUA submissions that are applicable to the full range of countermeasures (biologics, drugs, and devices).

Question 5. Under the animal efficacy rule used for approval of biodefense countermeasures, there is little guidance provided by the FDA to developers of these products about what the ultimate indication for the product will be. This is particularly true for therapeutics.

What is your view of the best way for FDA to provide enough guidance to these critical development efforts to ensure they are successful in obtaining the appropriate clinical data that will be required for licensure?

Answer 5. FDA has an important role in the Nation's effort to identify, prepare for, and respond to chemical, biological, radiological, and nuclear (CBRN) threats and incidents. To this end, we have a broad strategy for working closely with industry and with our Federal, State, and local partners to facilitate the development and availability of new medical countermeasures.

We encourage early interactions with sponsors interested in developing a new countermeasure or a new counterterrorism-related indication for a previously approved product. Based on feedback from industry, we believe that these interactions offer sponsors valuable technical assistance and expertise and can help to expedite

the development and successful approval of new countermeasures. Sponsors interested in developing a new countermeasure come to the Agency with a proposed indication for their product and the Agency then advises them with regard to the necessary data needed to achieve the desired indication.

DRUG DEVELOPMENT AND ACCESS

Question 6. In light of recent concerns over drug safety, how will the Agency best ensure safety without limiting patient access to lifesaving drugs?

Answer 6. All drugs have risks, and FDA reviewers balance these risks against identified benefits for each product. When a new drug application (NDA) is being reviewed, it is imperative that the drug's risks as well as its benefits be understood as thoroughly as possible. FDA has new industry guidance and internal initiatives for optimizing safety data collection during large phase III trials. In addition, new initiatives, such as the standardization of study variable names, the development of computer-based review tools to speed the identification of safety risks in NDA databases, the development of a safety template for use by FDA reviewers, and the Critical Path Program all promise to maximize the understanding of a drug's safety profile at the time of the NDA review.

This deeper understanding of a drug's risk profile allows FDA reviewers to make better informed benefit-risk evaluations. Decisions regarding drug approval always factor in the severity of the underlying disease, and the benefits and risks of potential alternative treatments. FDA understands that the American public will accept a higher risk of serious side effects when the drug effectively treats a life-threatening disease with few or no treatment alternatives (e.g., some types of cancer, AIDS).

In contrast, when there are many available beneficial and well tolerated drug alternatives for a disease or condition, FDA is more cautious about approval of new drugs with significant toxicity. For example, with the many well tolerated drugs available to lower cholesterol or blood pressure, a new drug for these purposes that was more toxic than the available drugs might ordinarily not be approved (or could be withdrawn) unless it could treat a resistant population (whose elevated risk of complications and/or death would make the extra risk of the drug acceptable).

At times, the judgment of whether the need for more safety data outweighs the need for a new effective treatment is controversial. In these cases, discussion at an FDA advisory committee meeting allows academia, the practice community and the public to share their knowledge and perspective on the benefit-risk balance and therapeutic need. This external advice helps guide FDA in its final decisionmaking.

In all cases, FDA works to ensure that a drug's risks have been well studied and that drug labeling reflects those risks and benefits. Effective communication between the Office of New Drugs and the Office of Surveillance and Epidemiology prior to drug approval and afterwards sets the foundation for shared monitoring of the new drug's identified and potential risks as it is introduced into the market.

Question 7. The cost and time of new product development has been a concern for patients as well as sponsors. What is the Agency considering doing to address these concerns in regards to trial size, duration, and patient accrual?

Answer 7. FDA is actively considering under the Critical Path initiative a variety of study designs, methods of analysis and uses of data from other studies to improve decisionmaking and the rate of success of studies. We continuously evaluate new clinical trial designs that hold the promise of more efficient drug development as well as nontraditional statistical approaches that may lead to more efficient drug development. For example, the appropriate use and applicability of historical controls in which the effect of a new treatment in a group of patients is compared to well-documented experience from other studies is considered in detail in the International Conference on Harmonization (ICH) guidance E-10 (Choice of Control Group and Related Issues in Clinical Trials.), and in certain circumstances such trials designs are employed to expedite drug development.

Under certain circumstances, we also have the authority to base a finding of substantial evidence of effectiveness on the results of a single adequate and well controlled clinical study rather than the more traditional two-study standard. This standard can help speed important new therapies to market by reducing the number of trials that must be performed to gain marketing approval. Also, under the law and regulations, we can approve drugs on the basis of their effects on a marker that is reasonably likely to predict a clinical benefit, provided that we are able to obtain evidence after approval to establish that the drug had clinical benefit. This approach is reserved for serious or life-threatening conditions for which there are inadequate available treatments. Although there are difficulties with this approach and it must

be used responsibly and with caution, where appropriate, it can drastically reduce the time to market for important new drugs.

Question 8. While the Director of NCI, you were instrumental in creating a joint task force with FDA to optimize the development and review process for new cancer drugs. Do you see the potential for other FDA-NIH partnerships that could be applied to other indications?

Answer 8. In 2003, Secretary Thompson, Dr. McClellan, and I announced a collaboration to streamline cancer drug development—the Interagency Oncology Task Force (IOTF). Under the agreement between the Food and Drug Administration (FDA) and the National Cancer Institute (NCI), an institute within the National Institutes of Health (NIH), the two agencies would share knowledge and resources to facilitate the development of new cancer drugs and speed their delivery to patients. Although FDA and 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. FDA's mission is to assure the safety, efficacy, and quality of manufacturing of new medical products prior to marketing. This interagency collaboration takes full advantage of their combined knowledge bases.

FDA and NIH recently announced the first major program from this collaboration entitled the Research and Regulatory Review Fellowship Program. The program is designed to train a cadre of researchers to bridge the processes from scientific discovery through clinical development and regulatory review of new oncology products. This program is a critical first step in establishing 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.

Staffs from both agencies continue to work jointly in other major areas under the IOTF umbrella. This effort will be crucial in fostering the new age of medical products to conquer cancer. Some of these products will include nanotechnology, clinical beneficial surrogate markers and chemoprevention.

I hope that this interagency prototype will serve as a model for other NIH and FDA collaborative efforts for other areas of research and drug development.

PLAN B ("MORNING AFTER PILL")

Question 9. FDA announced its intention to work with Duramed, the manufacturer of Plan B, to resolve the remaining policy concerns regarding the application for over-the-counter (OTC) status. Is there precedent for approving a drug for OTC use for a subset of the population solely based on age, but requiring a prescription for another set of the population? How will FDA enforce restrictions on OTC use of Plan B for women only over the age of 18? What requirements would be made for marketing Plan B for OTC use vs. prescription-only?

Answer 9. There are currently no other products approved for OTC use for one population based solely on age and by prescription for another population based solely on age, although non-prescription nicotine replacement therapy products are approved only for consumers 18 and older.

Duramed has agreed to conduct a "Point-of-Purchase Monitoring Program" to track how Plan B® is being sold at the time of purchase. Using the data collected, the sponsor agrees to document and analyze the level of comprehension of the Plan B® prescription age requirement and how it is handled at the point of purchase. The program will be conducted twice in the first year and annually thereafter. The sponsor also agreed to report repeat violators to the relevant State Boards of Pharmacy. Finally, the sponsor committed to report to FDA on the results of these activities on a 6-month interval beginning 30 calendar days after the 6-month interval commencing on the date of the approval of the amended sNDA. Monitoring of the program's effectiveness will allow FDA to assess whether further modifications will be necessary to prevent inappropriate use of Plan B®. Additional details of the other commitments made by the sponsor to support the OTC marketing of Plan B may be found on FDA's Website at *http://www.fda.gov/cder/drug/infopage/planB/default.htm.*

iPLEDGE RISK MANAGEMENT PROGRAM

Question 10. A bipartisan letter on the iPLEDGE program was co-authored by me and my colleague Senator Durbin and sent to you recently. Senators Roberts, Hatch and Dodd—colleagues on this committee—joined Senators Bennett, Wyden, and Feingold on this letter. Hundreds of dermatologists and their isotretinoin (Accutane) patients have contacted us to share their frustrations and concerns with the iPLEDGE program. It is essential that stakeholders like prescribers and patients

be involved at every step of the process to ensure continued access to this valuable medication.

Can you tell me what specific steps FDA is taking to guarantee that stakeholders are involved in a meaningful way in the process of developing iPLEDGE program features, and reviewing and updating the iPLEDGE program? There is a paucity of data on the incidence of severe nodular cystic acne in the United States. What data did FDA use in its review and approval of the iPLEDGE program?

Answer 10. iPLEDGE is intended to ensure that isotretinoin is prescribed and dispensed under conditions of safe use. Thus all patients, whether being treated for severe recalcitrant nodular acne or for recognized off-label uses (for example, neuroblastoma), need to be registered and activated in iPLEDGE to ensure that the risk of fetal exposure to isotretinoin is minimized. The data that FDA considered and presented in February 2004 to a joint meeting of the Drug Safety and Risk Management and Dermatologic and Ophthalmic Drugs Advisory Committees addressed the ability of the existing RiskMaps for isotretinoin products to prevent pregnancy. The existing programs included the System to Manage Accutane Related Teratogenicity (S.M.A.R.T.) and similar programs from generic drug manufacturers. After reviewing this data, the joint committees advised and FDA concurred that the programs in place at that time could be improved by having a single RiskMap for isotretinoin and more stringent controls to include mandatory registration of all participants and to link negative pregnancy testing to prescription dispensing for female patients who can become pregnant. The Agency approved the labeling supplement for the iPLEDGE program on August 12, 2005. The specific data presented that led to these conclusions can be found on the Website for that Advisory Committee meeting.

FDA has taken several steps to guarantee stakeholder input into decisions made about how to manage the risks of using isotretinoin. First, stakeholders had input into the decisions regarding the design of iPLEDGE. Input from outside interested parties was solicited and heard at the February 2004 joint Advisory Committee at which FDA presented its assessment of previous programs to reduce the risk of fetal exposure to isotretinoin.

Second, once the decision was made to modify the risk management plan for isotretinoin, we sought stakeholder input into how best to implement it. Covance, the sponsor's vendor, convened a Scientific Advisory Board in March 2005 to obtain stakeholder input on iPLEDGE. The Scientific Advisory Board meets regularly to provide stakeholder input on iPLEDGE issues and future updates. Additionally, both Covance and the FDA have participated in professional meetings of various stakeholder groups such as the American Academy of Dermatology, the National Association of Chain Drug Stores, and the Health Distributors Management Association.

Question 11. I brought to FDA's attention a young woman from New Hampshire who was prevented from filling her prescription of isotretinoin due to systemic problems in the iPLEDGE program. FDA was instrumental in ensuring that the young women's prescription was filled even though the iPLEDGE system denied her access to the drug.

What is FDA doing to improve the operation of this program and ensure that its risk management goals are met?

Answer 11. FDA has worked closely with isotretinoin sponsors and their vendor, Covance Inc., to maintain a critical balance between access to the drug by patients who need it and ensuring its safe use. In response to concerns raised by dermatologists and pharmacists in recent weeks, FDA has ensured that rapid and significant progress has been made by the sponsors and Covance to address operational aspects of the program. Specific measures taken include an increase in iPLEDGE call center staffing to handle the expected increases in call volume and user questions, as well as an enhanced system to process requests for new passwords by users who have forgotten or lost their original passwords.

Question 12. The drug company sponsors of the iPLEDGE program (known collectively as the Isotretinoin Products Manufacturing Group, or IPMG) stopped providing free isotretinoin to indigent patients with the launch of the iPLEDGE program. Promoting access to this medication for all patients qualified to take it is an important issue. Is the Agency taking action to promote the renewal of the free medication program? If not, why not?

Answer 12. Provision of free medication for indigent patients was not prohibited as a result of the iPLEDGE program launch. Decisions to provide free medication for indigent patients lie solely with the sponsors and are not under FDA purview.

MEDICAL DEVICES

Question 13. During the SARS epidemic, the Administration urged the device industry to develop a rapid SARS diagnostic test and several companies agreed to pursue development of a test. However, those companies were never able to obtain SARS biological samples in order to develop tests. The problem still exists today for pandemic influenza and may hamper development of point of care diagnostic pandemic influenza tests. The device industry has proposed that a process be established for emerging biohazards and threats—similar to that used during the West Nile Virus outbreak—that would establish regular meetings between FDA and CDC and interested industry stakeholders and require the adoption of processes for sharing samples needed to develop tests for emerging infectious diseases. Would you be willing to work toward such a process?

Answer 13. The Agency will work with all stakeholders and interested parties to assist in sharing information and samples that will advance this field.

Question 14. A second barrier that may hinder the development of potentially lifesaving medical product countermeasures is FDA's requirement that original samples be used for the review or approval of a medical product countermeasure. I understand, however, that in the case of the West Nile virus, detection medical devices received approval conditioned on a requirement to provide post-clearance data. Given that this uncertainty surrounding product approval will be an ongoing problem with emerging infectious diseases, is it appropriate for FDA to develop an approval process using virus isolates conditioned upon a requirement to provide post-clearance data to ensure that safe and efficacious products are developed and reviewed or approved?

Answer 14. FDA is willing to work with sponsors to determine the least burdensome methods of generating data to support pre-market review and satisfy the legal requirements for clearance or approval of diagnostic devices for emerging infectious diseases.

When prospective clinical samples are difficult to obtain, in some cases FDA is able to accept information obtained with spiked samples to support analytical claims and with banked samples to support clinical claims. Post-market studies are not used to replace the pre-market review process for establishing the safety and effectiveness or substantial equivalence of new devices. These studies, however, can be very helpful in gathering data to refine use of a new test. For PMA products, post-market studies can be ordered as a condition of product approval.

In cases in which there is insufficient data to establish the safety and effectiveness or substantial equivalence of a new diagnostic device, FDA can work with sponsors to ensure availability of tests with appropriate patient safety controls using Investigational Device Exemption (IDE) submissions, or in cases of actual potential emergency can use the Emergency Use Authorization (EUA), if statutory criteria are met, to ensure availability of critically important cutting edge diagnostics for public health use.

BLACK BOX WARNINGS

Question 15. In its Drug Safety report released earlier this year, the GAO found that "there is a lack of criteria for determining what safety action to take and when to take them," and cited the imposition of "black box warnings" as an example. If confirmed, what action would you take to address concerns raised by GAO?

Answer 15. FDA's Center for Drug Evaluation and Research (CDER) has already embarked on many improvement efforts to address the points made by the GAO report entitled, "Drug Safety: Improvement Needed in FDA's Post-market Decision-Making and Oversight Process." FDA continues to build upon these efforts. For instance, the Agency asked the Institutes of Medicine (IOM) to perform a study on drug safety, aiming to evaluate the drug safety system in the United States and to assess what additional steps could be taken to provide more certainty about drug side effects. This study is nearing completion. I will ensure that the recommendations are carefully considered as we work to improve Agency actions on drug safety issues.

Additionally, in January, the Agency published two documents on the presentation of risk information in professional labeling for prescription drug products to assist drug manufacturers in communicating drug safety information through labeling:

- Final guidance to industry, "Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format" to aid in the selection, characterization, organization, and updating of information in the Adverse Reactions section; and

• Draft guidance to industry, "Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format" to seek comment on proposals on when and what information should be included in these sections. This document may be accessed online at: *http://www.fda.gov/cder/guidance/5538dft.pdf.*

In addition, FDA implemented changes in how drug safety is assessed in CDER. As an example, CDER's Office of Surveillance and Epidemiology (OSE) and Office of New Drugs (OND) have initiated routine, periodic safety meetings to discuss ongoing post-marketing safety issues and to ensure effective communication and efficient prioritization of work. This effort is one response to work that OND and OSE have been doing using internal process improvement teams in place to clarify roles and responsibilities and standardize processes for staff working on post-marketing safety issues.

Finally, CDER has established a clear pilot program to provide a new mechanism to ensure that the opinions of scientific reviewers are incorporated into the decisionmaking process, in CDER's Manual of Policies and Procedures (MAPP) 4151.2, Documenting Differing Professional Opinions and Dispute Resolution—Pilot Program. This document is available online at: *http://www.fda.gov/cder/mapp/4151.2.pdf.*

EVALUATING 21ST CENTURY SCIENCE

Question 16. The FDA created the Critical Path Initiative to identify opportunities in modernizing new product development. What are your priorities for making the March 2006 C-Path Opportunities Report a reality?

Answer 16. The critical path initiative is a high priority for the Agency. In fact, we have made this initiative a top priority in the fiscal year 2007 budget. We have been able to initiate projects in all six priority areas discussed in the Opportunities Report and List. In the next month, we will publish a followup report describing specific Critical Path projects we are undertaking in calendar year 2006.

More important, our over-arching priority is to reach beyond specific opportunities and build public and private collaborations to work together to encourage continued development of the Critical Path sciences. As Secretary Leavitt noted when we released the List and Report, "The power of public-private partnerships is vital to accomplish the tasks set forth in the Critical Path Opportunities List." For additional information about the critical path initiative, please see the FDA web page entitled, "The Critical Path to New Medical Products," *http://www.fda.gov/oc/initiatives/criticalpath/*.

Question 17. Recent discoveries such as the completion of the human genome project have the potential to lead to advanced techniques and products that could revolutionize treatments for patients. How is FDA preparing to keep up with the associated new regulatory challenges?

Answer 17. Completion of the human genome project has provided a unique opportunity to identify sources of inter-individual variability in drug response (both efficacy and toxicity) and identification of biomarkers for biologic product quality. This unique approach will help individualize therapy with the intent of maximizing effectiveness and minimizing risk. FDA scientists have developed a multifront strategy to meet the regulatory challenges of the post-genome era. One example is FDA's "Guidance for Industry: Pharmacogenomic Data Submissions" intended to facilitate scientific progress in the field of pharmacogenomics and facilitate the use of pharmacogenomic data in regulatory decisionmaking. Another strategy is continuing education of regulatory scientists at FDA through hands-on training, workshops, and off-site visits to leading genomics-oriented companies. FDA is currently accepting Voluntary Genomics data submissions (VGDS) not associated with regulatory applications for product development in order to facilitate application of the technology and provide hands on learning and discussions between FDA regulatory scientists and industry. In addition, we have formed a Genomics and Proteomics working group to coordinate all genomics activities across the FDA.

Some initiatives underway to aid in the development of partnerships with stakeholders to standardize the acquisition, quality, storage and exchange of data include: unique outreach to regulated industry to encourage submissions using joint interpretations of data from new technologies promising for the regulatory process; and, where appropriate, research partnerships to evaluate the utility of emerging technologies in evaluating safety and efficacy of regulated products. The stakeholders include scientists from every aspect of the scientific enterprise including: regulatory scientists from other government agencies, academicians engaged in discovery research, scientists from applications industries, as well as scientists in regulated industry. Examples of partnerships include: an intra-Agency consortia (pri-

marily between NCTR and CDER) to receive and secure regulatory data, development of technical standards for application of genomics technology in medical research, data organization, integrity characteristics and analysis; characterization of quality control parameters for effective comparison of results across commercial analytical products; CRADAs for co-exploration of emerging technology to predict health and disease; and CRADA for the characterization of cell substrates used for the production of vaccines, blood and blood components and cell and gene therapy products.

In addition, in order to provide effective regulatory review of biological products, the Center for Biologics Evaluation and Research (CBER) conducts mission-related research programs. This research greatly expands our knowledge of fundamental biological processes and provides a strong scientific base for regulatory review. For example, CBER is conducting research to find genes that control development of inhibitors against factor VIII in hemophilia patients as part of understanding the safety and efficacy of hemophilia therapy. This research utilizes the benefits derived from the human genome project, in which the variable sites in the human genome have been cataloged and methods for analysis of a large number of polymorphic sites in the genome were made possible.

Question 18. As you know, the FDA Modernization Act sought to provide the Agency with new tools to address the rapidly changing technologies associated with medical devices. With the rapid advancement of science, including genomics and proteomics, soon it may be possible to prevent disease before it starts, treat those at risk preemptively, and develop personalized treatments for those who do fall ill. What new tools will FDA need to transform FDA's current approval process to evaluate 21st century science?

Answer 18. As previously stated, the FDA of the 21st Century must incorporate modern management tools and processes to meet the challenges of today, while creating the scientific tools and technologies to address the ever-evolving, increasingly complex issues of the future. To accomplish this task, FDA will require 21st Century IT infrastructure and personnel expertise to manage and interpret the data from modem technology. Additionally, we will continue working diligently to assure proper development of guidance, proper modifications of regulations (when appropriate) and proper staffing to assure rapid review of new technology.

The Critical Path Initiative is FDA's effort to stimulate and facilitate a national effort to modernize the scientific process through which a potential human drug, biological product, or medical device is transformed from a discovery or "proof of concept" into a medical product. Through this Initiative, FDA took the lead in the development of a Critical Path Opportunities List and Report to describe and provide examples of how new scientific discoveries—in fields such as genomics and proteomics, imaging, and bioinformatics—could be applied to improve the accuracy of the tests we use to predict the safety and efficacy of investigational medical products. Additional information about the critical path initiative, including the List and Report, may be accessed at *http://www.fda.gov/oc/initiatives/criticalpath/*.

Question 19. FDA is working on adaptive clinical trial techniques, which will result in a clearer indication of who can benefit from the drug and a narrower indication. Will this type of drug development produce drugs with which we will have greater confidence in safety?

Answer 19. There are many aspects to the adaptive trial approach. One approach may be to better target those study subjects that may be at higher (or lowered) risk for certain adverse events. Another way may be to better differentiate patient subpopulations with improved benefit/risk profiles.

With the use of prospectively adaptive study designs, researchers may be able to select a promising dose regimen that may help minimize safety concerns or increase chances of success for late phase drug development. These types of designs may allow the sponsor to drop doses early on in the process that may be cause for safety concerns or lack of effect. This approach is more likely to produce a final tested regimen that will be both safe and effective. FDA is very interested in discussing adaptive trial design strategies with drug developers in an effort to foster innovation and increase drug development efficiency.

RESPONSE TO QUESTIONS OF SENATOR BURR BY ANDREW C. VON ESCHENBACH

Question 1. Can you please update the committee on the efforts the Agency is taking, in advance of the September 30th effective date of the Combat Meth Act, to implement that statute and its provisions addressing pseudoephedrine-based meth diversion?

Answer 1. While the primary responsibility for implementation of the Combat Meth Act is with the Department of Justice (DOJ), FDA has acted to ensure regulated industry understands its obligations with respect to FDA-regulated products. Immediately after enactment, we provided manufacturer and drug information to the Drug Enforcement Administration (DEA) needed for DEA's rulemaking on manufacturer production and import quotas, part of the Combat Meth Act.

Also, the Office of Non-Prescription Products (ONP) is interacting with manufacturers to help them interpret the Combat Meth Act provisions for packaging of both NDA and OTC monograph products. For example, OTC products that are marketed under the OTC Drug Review may be reformulated following the stipulations for active ingredients, manufacturing, and labeling that are set out in the regulations associated with the OTC monographs. These reformulations do not require approval by the FDA prior to marketing. Accordingly, an immediate release tablet containing pseudoephedrine as a decongestant in combination with an antihistamine could be reformulated under the monograph to contain an alternative decongestant, phenylephrine, in combination with the same antihistamine. This reformulation would not require prior approval, supporting a rapid transition from products containing pseudoephedrine to products using other antihistamines. In addition, a new salt of phenylephrine was recently added to the monograph to allow manufacturers more flexibility in formulating products.

In addition, OTC products that are marketed under New Drug Applications (NDAs) require FDA review and approval prior marketing of a reformulated product. Such supplementary applications are reviewed under the specific timelines and procedures associated with the Prescription Drug User Fee Act (PDUFA) and other pertinent regulations. ONP interacts with applicants to insure that only essential testing is required to demonstrate that the reformulations will be safe and effective. For instance, applicants would, in general, not be required to conduct clinical trials to demonstrate the safety and effectiveness of a product reformulated to include phenylephrine in place of pseudoephedrine. Applicants would instead be able to demonstrate the bioequivalence of the new product in humans compared to reference standards, a lesser demand on applicant resources.

Question 2. As you know, the Senate Appropriations Committee Report on the fiscal year 2007 FDA Appropriations Bill (like the House Appropriations Committee Report) includes an "Expedited Filing" provision that directs the Commissioner to encourage, expedite, and support the filing, review, and final action on any new drug application, or supplement to a new drug application, seeking approval of a combination of active ingredients previously approved as safe and effective, that would replace or provide a therapeutic alternative to a currently-marketed drug product that contains an active ingredient that currently is the subject of diversion and/or abuse outside regulated channels of commerce. In the context of this Appropriations provision, would you please delineate for the committee the steps that the Agency has taken to enhance access to new prescription combinations of safe and effective marketed drugs that could provide alternative therapies to replace pseudoephedrine-containing products and address major public health and safety concerns arising from meth production?

Answer 2. Products which require New Drug Applications (NDA) or a supplement to an NDA (SNDA) may qualify for a priority review. We will meet with applicants to determine if such applications qualify to be considered under priority review. The ability to actually develop such a formulation and provide data to demonstrate that it is abuse resistant (and not simply defeatable by another mechanism) is complex. We interact with such applicants to ensure that only essential testing is required to demonstrate that the reformulations will be safe and effective. For instance, clinical trials are not required in any instance in which a demonstration of bioequivalence in humans can be appropriately applied. This may help shorten the time necessary to provide data for the NDA or SNDA. We also will respond to submissions and meeting requests quickly so that access is not delayed based upon the ability of a company to get feedback or to interact with the Agency.

RESPONSE TO QUESTIONS OF SENATOR DEWINE BY ANDREW C. VON ESCHENBACH

Question 1. What kind of restrictions will be in place to ensure that Plan B does not end up in the hands of children under 18?

Answer 1. Duramed has agreed to conduct a "Point-of-Purchase Monitoring Program" to track how Plan B® is being sold at the time of purchase. Using the data collected, the sponsor agrees to document and analyze the level of comprehension of the Plan B® prescription age requirement and how it is handled at the point of purchase. The program will be conducted twice in the first year and annually there-

after. The sponsor also agreed to report repeat violators to the relevant State Boards of Pharmacy. Finally, the sponsor committed to report to FDA on the results of these activities on a 6-month interval beginning 30 calendar days after the 6-month interval commencing on the date of the approval of the amended sNDA. Monitoring of the program's effectiveness will allow FDA to assess whether further modifications will be necessary to prevent inappropriate use of Plan B®. For details of the other commitments made by the sponsor to support the OTC marketing of Plan B®, see the attached approval letter, labeling, and the CARE program.

Question 2. What penalty, if any, will there be for manufacturers or distributors who distribute Plan B to children under 18?

Answer 2. The sponsor committed to report to FDA on the results of its point-of-purchase monitoring program on a 6-month interval beginning 30 calendar days after the 6-month interval commencing on the date of the approval of the amended sNDA. In addition, the sponsor agreed to report repeat violators to the relevant State Boards of Pharmacy. Monitoring of the program's effectiveness will allow FDA to assess whether further modifications will be necessary to prevent inappropriate use of Plan B®.

Question 3. What penalty, if any, will there be for pharmacies or pharmacists who distribute Plan B to children under 18?

Answer 3. The same penalties that would apply to any pharmacy or pharmacists who dispense a prescription product without a valid prescription would apply.

Question 4. The Best Pharmaceuticals for Children Act (BPCA), passed in 2002, has resulted in more than 100 changes to drug labels reflecting pediatric information. BPCA is due to be reauthorized next year, what proposals would you make for strengthening this important legislation to produce an even greater number of drugs labeled for children?

Answer 4. I believe that BPCA has been an important tool in obtaining needed pediatric information to treat pediatric patients. We have been reviewing possible improvements that could make the program even more effective. Our review is not yet complete. If we determine new legislative proposals are necessary, we look forward to working with you to enhance the program.

Question 5. BPCA encourages pediatric drug studies by providing an additional 6 months of patent protection to a drug if sponsors respond satisfactorily to a written request by FDA. Several proposals in Congress have been made to limit the patent extension or to "tier" the length of the extension based on the sales of the drug. What would be the effect of such proposals on the number of pediatric drug studies conducted? Does FDA have the capacity to administer a system where exclusivity extensions are "tiered?"

Answer 5. We understand that there are a number of proposals being discussed by external groups to change the way the pediatric exclusivity period is implemented. We have not yet evaluated these proposals in detail. As we approach reauthorization next year, our primary concern will be to ensure that (1) the program remains effective in getting drug products labeled for pediatric use, and (2) FDA is not given additional burdens or responsibilities that we are unable to handle within our public health mission and level of funding.

Question 6. The European Union recently adopted legislation to encourage testing and development of drugs for children. Did the European Union consult FDA in the development of this legislation? How does the EU model differ from the United States' approach to pediatric drug development and testing? In particular, how does the EU approach to studying generic drugs for children differ from the United States?

Answer 6. The EU regulation for pediatric product development, which will be implemented later this year, combines the incentive aspects of BPCA and the requirement aspects of PREA into one regulation. Prior to finalizing the amendments the European Medicines Agency (EMEA) consulted with FDA on numerous occasions concerning U.S. pediatric initiatives.

FDA does not yet have a detailed analysis on all of the differences between the U.S. and EU approach to studying innovator and generic drugs for children, but can provide some general information on the overall EU pediatrics program. The EU model provides a mechanism to obtain pediatric information on products with marketing protection (on-patent products), products with no marketing protection (off-patent products), and orphan products. There also is a post-marketing mandate that obligates sponsors to monitor efficacy and adverse drug reactions of all products approved for pediatric indications within 2 years of approval.

The EU model has many similarities to the U.S. approach. Both include an incentive for conduct of pediatric studies, both require that sponsors conduct certain studies, and both provide a mechanism for waivers and deferrals. Some key provisions are:

• The EU approach requires that all products seeking a marketing approval ("authorization"), with or without a pediatric indication, will go through a Pediatric Committee which will work to develop the Pediatric Investigational Plan (PIP). The incentive cannot be awarded unless the studies are consistent with the PIP.

• Under the EU system, the Pediatric Committee will be primarily responsible for the scientific assessment and development of the PIP and for administering the system of waivers and deferrals. In the United States, the BPCA process and the PREA process operate with less centralization. Written Requests issued by the FDA under BPCA, are drafted by the review divisions and reviewed by a central review team called the Pediatric Implementation Team (PDIT). The review divisions also determine the studies required for and the availability of waivers and deferrals under PREA.

• Under the EU system, products not covered by a patent or a supplementary protection certificate may qualify for a new type of authorization called a "Pediatric Use Marketing Authorisation" or PUMA. This provides 10 years of data protection, use of the existing brand name (brand name recognitions) and a symbol on the label indicating the product has been studied for this indication in pediatrics.

• All EU products which have participated in the pediatric process will be identified on their labels with a symbol that will indicate the product has been studied in the pediatric population.

• Under the EU system, orphan products can obtain an additional 2 years of marketing exclusivity for studies conducted in the pediatric population. In the United States, these products would be eligible for 6 months marketing exclusivity.

Question 7. The Pediatric Research Equity Act (PREA) is also due to be reauthorized next year. PREA has been successful in making pediatric studies a routine component of a new drug application or supplement. Does FDA track the number, types of studies and labeling changes resulting from PREA?

Answer 7. PREA was passed into law on December 3, 2003 and is retroactive to April 1, 1999. Preliminary numbers indicate that for applications submitted to the Agency since April 1, 1999, 286 applicants have fulfilled their pediatric studies requirements under PREA for CDER. CDER has granted 570 waivers of pediatric studies and 429 deferrals of pediatric studies pursuant to PREA provisions. We do not have a specific combined tracking system for the numbers and types of studies from each division. We are now in the process of compiling labeling changes that resulted from PREA studies and expect to be able to publicly post these labeling changes to our pediatric Website by the end of this year. Studies that have been deferred upon approval of the drug are listed in the Post-Marketing Study Commitments Database that can be located on the CDER Website. The Center for Biologics Evaluation and Research (CBER) had 16 approved Biologics License Applications (BLA) and Biologics License Supplements (BLS) submissions received from April 1, 1999 through August 21, 2006 which included the complete required pediatric studies. Since April 1, 1999, CBER has granted 24 deferrals and 5 waivers.

Question 8. FDA does not have explicit authority to distinguish on a label whether a product has been studied in children and found not to be effective or if it has not been studied in children. Is explicit legislative authority necessary and, if granted, how would it improve the speed of labeling changes? Are there other resources or authorities FDA needs to reduce the time it takes for pediatric information to be included on a drug label?

Answer 8. Increasingly, product labeling is being used to convey the current state of knowledge about the safety and efficacy of a drug in the pediatric population. We already have begun to implement an effort to ensure that label changes are made for all drugs for which studies are submitted under BPCA. These labeling changes aim to ensure that products studied under BPCA have labeling that includes more information than the statement "safety and efficacy had not been established in the pediatric population." Thus, where a study is inconclusive about safety or effectiveness, the labeling may describe the results of the study without stating that the drug should or should not be used in certain pediatric populations. Similarly, if FDA has information that establishes that a drug does not work in pediatric populations or if clinical trials reveal a safety concern, FDA would place that information in the labeling, even if the drug is not approved for use in the pediatric population.

Section 5 of the BPCA provides a process for timely labeling changes for drugs granted exclusivity, including a provision for referral to the Pediatric Advisory Com-

mittee. Although this process does not apply to labeling changes for studies performed under BPCA where exclusivity was not granted, nor for studies conducted outside of the scope of BPCA, we have moved forward to ensure sufficient information will be included in the label. The changes made in BPCA have been of great assistance in ensuring more prompt agreements once the supplement has been reviewed and acted on by FDA.

There is also legislative authority granted by PREA that allows us to require sponsors to include information in their label indicating that pediatric studies were waived because they believe the drug would not be effective in pediatric patients or because there are safety concerns for pediatric patients.

FDA acknowledges that we use various terminologies in labeling to describe the results of studies, some of which may not convey, as clearly as one might hope, if data were collected in pediatric patients. FDA is working to improve the clarity of pediatric information included in labeling and will continue to do so.

Question 9. Cutting-edge research and revolutionary technologies have led to the development of countless innovative medical devices, allowing patients to live longer, healthier lives. However, as science and medicine move forward, children are at risk of being left behind. Too few critical medical devices are designed specifically with children's needs in mind. What efforts are being made by FDA to increase the access of children to appropriate medical devices?

Answer 9. Although cutting-edge research and revolutionary technologies have led to the development of new innovative devices, pediatric device development faces additional challenges that may cause it to lag behind adult device development. The type of applicants (small companies) and obstacles to the development of pediatric devices, including the difficulties in conducting device clinical trials involving children, make this issue extremely challenging. FDA believes that communication between the Agency, industry, patients, and clinicians is essential for fostering pediatric device innovation. To this end, CDRH has been focusing on increasing interactions among these parties during product development and pre-market review. Examples include:

- CDRH is working to develop more device-specific guidances that would, when appropriate, include advice for manufacturers on issues such as the type of modifications, testing, and/or labeling changes needed for the device to be used in pediatric populations.
- CDRH is holding workshops to discuss the development of critical pediatric devices. In 2005, CDRH held an advisory panel meeting to discuss clinical trial designs for, and ethical issues related to, the evaluation of devices to treat pediatric obesity. In 2006, FDA sponsored a workshop for manufacturers of pediatric left ventricular assist devices intended for infants and children from 2 kg to 25 kg with congenital or acquired cardiovascular disease. Finally, in collaboration with NIH, CDRH held a public workshop to identify new approaches to evaluating fetal intrapartum monitoring devices, including the possible development of a large validated test database.
- As part of FDA's Critical Path Initiative, CDRH is collaborating with the Juvenile Diabetes Research Foundation to accelerate development of an artificial pancreas for children with diabetes by creating new clinical protocols and improved outcome measures for evaluating the performance of continuous glucose sensors and a closed loop artificial pancreas.

Question 10. Is FDA currently tracking the number of devices approved for children each year along with the need for such devices? If not, why not?

Answer 10. FDA does not have a data system capable of tracking all studies, submissions, or approvals for pediatric devices, but as discussed below, we have made important strides in this area. Some medical devices are specifically designed for use on infants and children, such as infant incubators and infant radiant warmers, and each has a unique classification regulation associated with it. For these devices, we are able to identify the number of applications that have been cleared or approved. Under a provision in the Medical Device User Fee and Modernization Act of 2002, device submissions solely for pediatric use are exempt from user fees in order to encourage their development. FDA's user fee database allows us to identify those applications that seek to take advantage of this incentive. Most medical devices, however, are indicated for general use, which often includes pediatric use with the only difference being the size of the device available. Since these devices can be used in both the pediatric and adult populations, these are not specifically tracked as pediatric devices.

CDRH believes there are potential advantages in being able to track pediatric device submissions and approvals, and we are modifying our tracking systems to ac-

complish this. For instance, in addition to tracking the number of marketing clearances/approvals for pediatric devices, tracking the number of submissions of Investigational Device Exemption (IDE) applications would allow us to report how many studies of pediatric devices are currently ongoing. CDRH is currently making these database changes, so that we will be able to track the number of PMAs, HDEs, and IDEs for pediatric indications in the near future.

In addition, FDA believes there may be value in tracking pediatric subpopulations (neonates, infants, children adolescents) for both marketing and investigational applications. We are examining whether and how our current database can accommodate such tracking, as well as determining the resources necessary to making such changes

Question 11. Does FDA agree with the findings and recommendations in the Institute of Medicine's July 2005 report, "Safe Medical Devices for Children," on adverse event reporting, monitoring of post-market study commitments, strengthening post-market studies and responsibilities for medical device safety? What actions have FDA taken to implement IOM's recommendations?

Answer 11. The FDA agrees that post-market surveillance of pediatric devices needs to be improved, and has taken a number of steps in this area. With regard to reporting of adverse events, FDA has been working to improve its capabilities to receive adverse event information for all devices electronically. Rapid development and implementation of these systems would enable the Agency to quickly identify and address post-market problems and elevate the quality of information and data received by using automatic error-checking routines. Currently, CDRH receives over 200,000 reports each year. These reports are manually entered into the FDA database at a cost of over $2.5M annually. Electronic Medical Device Reporting (eMDR) will allow electronic data entry and processing of all post-market medical device adverse event information. Cost-benefit analyses show that eMDR can save a significant portion of the data-entry cost, with potential for increased savings longterm. In addition, reports will be available for review and action immediately after submission. FDA's MedSun Program is also well-positioned to strengthen device-related surveillance and safety activities.

The IOM also recommended that the FDA improve the procedures for monitoring the status of post-market study commitments. Beginning in early 2005, the Center instituted a new electronic tracking system and draft guidance entitled "Procedures for Handling Post-Approval Studies Imposed by PMA Order." FDA intends to post the status of these studies on the Agency's Website. These changes will enable FDA—and the public—to better monitor the progress of the trials and the submission of required status reports.

FDA has also strengthened its post-market studies and responsibilities for medical device safety in several ways. The Center has expanded use of its epidemiologists and pediatricians during the pre-market review process. The epidemiologists have also helped to: develop a comprehensive plan for monitoring devices postmarket; determine the need for post-approval studies; lead the design of the post-approval study protocols; and work interactively with the sponsors to finalize the post-approval study protocols at the time of device approval. After device approval, epidemiologists continue to closely monitor the progress of the studies and critique interim and final reports. The Center is also planning periodic presentations to Advisory Panels on the status of post-approval studies.

Question 12. As you know, FDA is one of the key Federal agencies that must be in constant readiness for the next public health threat—the risks that have yet to blossom into full blown challenges. Drug-resistant infections like MRSA (methicillin-resistant Staphylococcus aureus) are epidemic. CDC says 60,000 to 80,000 Americans die every single year from hospital-acquired infections like MRSA. What is FDA doing about this infectious disease threat?

Answer 12. FDA provides regulatory guidance to sponsors to facilitate the development of drugs to treat infections caused by resistant pathogens such as methicillin-resistant Staphylococcus aureus (MRSA). Drugs for the treatment of MRSA infections are often eligible for Fast Track designation and/or priority review because MRSA infections may be serious and life-threatening and products that treat MRSA infections may address an unmet medical need.

There have been several drugs that have garnered approval of clinical indications that include MRSA as one of the listed bacterial pathogens within the indication. These include:

(a) Pfizer's product Zyvox® (linezolid) for the following indications: nosocomial pneumonia and complicated skin and skin structure infections, including diabetic

foot infections; both indications include MRSA as one of the listed bacterial pathogens.

(b) Wyeth's product Tygacil™ (tigecycline) for complicated skin and skin structure infections includes MRSA among the listed bacterial pathogens.

(c) Cubist's product Cubicin® (daptomycin) for complicated skin and skin structure infections and the recently-approved indication of Staphylococcus aureus bloodstream infections, both indications include the bacterial pathogen MRSA.

FDA conducted priority reviews for these products, committing resources to make these products available more quickly, while still ensuring their safety and effectiveness.

Question 13. Pseudoephedrine (PSE) is a safe and effective decongestant in many over-the-counter (OTC) medicines for treatment of the common cold and hay fever. However, PSE also is a precursor chemical being diverted to illicit manufacture of methamphetamine. Addressing this critical public health and safety problem necessitates transitioning consumers relying on PSE-containing OTC products to therapeutically-equivalent replacements that cannot be used in meth production.

During 2005, the Congress took action, reflected in the Conference Report on the Combat Meth Act, to facilitate FDA approval of such reformulated OTC products. Some longstanding OTC medicines that currently contain PSE and are marketed under the applicable FDA monograph potentially can be reformulated to include an alternate active ingredient in accordance with the steps Congress took in the Combat Meth Act.

In approaching the September 30th effective date of the Combat Meth Act, Congress understands there is a similar opportunity to facilitate development of new prescription products that could be approved by FDA as safe and effective therapeutic alternatives to fill the need currently met by PSE that could provide similar therapeutic benefits and be equally convenient—but without the diversion or abuse risks associated with PSE.

Can you please update the committee on the efforts the Agency is taking, in advance of the September 30th effective date of the Combat Meth Act, to implement that statute and its provisions addressing pseudoephedrine-based meth diversion?

Answer 13. While the primary responsibility for implementation of the Combat Meth Act is with the Department of Justice (DOJ), FDA has acted to ensure regulated industry understands its obligations with respect to FDA-regulated products. Immediately after enactment, we provided manufacturer and drug information to the Drug Enforcement Administration (DEA) needed for DEA's rulemaking on manufacturer production and import quotas, part of the Combat Meth Act.

Also, the Office of Non-Prescription Products (ONP) is interacting with manufacturers to help them interpret the Combat Meth Act provisions for packaging of both NDA and OTC monograph products. For example, OTC products that are marketed under the OTC Drug Review may be reformulated following the stipulations for active ingredients, manufacturing, and labeling that are set out in the regulations associated with the OTC monographs. These reformulations do not require approval by the FDA prior to marketing. Accordingly, an immediate release tablet containing pseudoephedrine as a decongestant in combination with an antihistamine could be reformulated under the monograph to contain an alternative decongestant, phenylephrine, in combination with the same antihistamine. This reformulation would not require prior approval, supporting a rapid transition from products containing pseudoephedrine to products using other antihistamines. In addition, a new salt of phenylephrine was recently added to the monograph to allow manufacturers more flexibility in formulating products.

In addition, OTC products that are marketed under New Drug Applications (NDAs) require FDA review and approval prior marketing of a reformulated product. Such supplementary applications are reviewed under the specific timelines and procedures associated with the Prescription Drug User Fee Act (PDUFA) and other pertinent regulations. ONP interacts with applicants to insure that only essential testing is required to demonstrate that the reformulations will be safe and effective. For instance, applicants would, in general, not be required to conduct clinical trials to demonstrate the safety and effectiveness of a product reformulated to include phenylephrine in place of pseudoephedrine. Applicants would instead be able to demonstrate the bioequivalence of the new product in humans compared to reference standards, a lesser demand on applicant resources.

Question 14. As you know, the Senate Appropriations Committee Report on the fiscal year 2007 FDA Appropriations Bill (like the House Appropriations Committee Report) includes an "Expedited Filing" provision that directs the Commissioner to encourage, expedite, and support the filing, review, and final action on any new

drug application, or supplement to a new drug application, seeking approval of a combination of active ingredients previously-approved as safe and effective, that would replace or provide a therapeutic alternative to a currently-marketed drug product that contains an active ingredient that currently is the subject of diversion and/or abuse outside regulated channels of commerce. In the context of this Appropriations provision, would you please delineate for the committee the steps that the Agency has taken to enhance access to new prescription combinations of safe and effective marketed drugs that could provide alternative therapies to replace pseudoephedrine-containing products and address major public health and safety concerns arising from meth production?

Answer 14. Products which require New Drug Applications (NDA) or a supplement to an NDA (SNDA) may qualify for a priority review. We will meet with applicants to determine if such applications qualify to be considered under priority review. The ability to actually develop such a formulation and provide data to demonstrate that it is abuse resistant (and not simply defeatable by another mechanism) is complex. We interact with such applicants to ensure that only essential testing is required to demonstrate that the reformulations will be safe and effective. For instance, clinical trials are not required in any instance in which a demonstration of bioequivalence in humans can be appropriately applied. This may help shorten the time necessary to provide data for the NDA or SNDA. We also will respond to submissions and meeting requests quickly so that access is not delayed based upon the ability of a company to get feedback or to interact with the Agency.

Question 15. While both drugs and medical devices are used to diagnose and treat human illness, there are also significant differences between the two categories of FDA-regulated products that Congress recognized in drafting their respective statutory frameworks. Will you continue to treat medical device issues on their own merits and tailor medical device policies so as to recognize their unique features and unique role in medical practice?

Answer 15. FDA recognizes that there are important inherent differences between drugs and devices and these differences require unique regulatory approaches.

Whereas small changes in a drug compound can often have profound effects on its mechanism of action and therefore the product's safety and effectiveness, minor changes in devices can often be made without greatly altering the function of the device. CDRH's 510(k) pre-market notification regulations for lower risk devices allow many products which are "substantially equivalent" to existing, legally marketed devices, to reach the marketplace in an efficient manner, for example, based on pre-clinical bench and/or animal data alone. Every year CDRH clears thousands of new devices through this less-burdensome mechanism. FDA has also succeeded in applying the appropriate level of regulatory controls to assure the safety and effectiveness of combination products where there is a merging of devices and drugs.

How devices are used also requires us to tailor device-specific policies. For example, most drugs are administered orally or intravenously and a placebo is often indistinguishable to the patient and/or clinician in a clinical trial. However, devices often require surgical implantation or cause a physical reaction to the body which a patient and physician would be well aware of. In addition, device use (and hence safety and effectiveness) can often be affected by the experience and skill level of the user. These and other issues make device trial design and data interpretation especially challenging.

We also recognize the financial burden on sponsors when clinical trials require expensive operations or where the nature of the device requires particularly long follow-up. FDA's regulations and policies allow us to take these issues into consideration by providing ample latitude in defining what constitutes "valid scientific evidence."

In summary, our current device classification system allows us to apply different policies and regulations to products depending on their associated risk and/or equivalence to other similar products in a least burdensome way, thus enabling FDA to address the unique issues associated with medical devices.

Question 16. The FDA's Critical Path Initiative has potential to improve the development process for medical technologies and bring better devices to market faster. Yet most of FDA's projects under the Critical Path initiative are focused on drugs—very few are dedicated to medical technology development. Given that the device development process for drugs and devices are vastly different, will you work to ensure the Agency dedicates more projects to device issues?

Answer 16. I am committed to ensuring the Agency's Critical Path Initiative encompasses devices and work is underway in this area. For example, FDA has established partnerships with the Juvenile Diabetes Research Foundation to work toward

development of an artificial pancreas, with the Critical Path Institute to use genomics for better dosing decisions for anti-coagulants, and with the University of Utah on virtual models to evaluate coronary and peripheral vascular stents. The Agency is actively looking for other collaborative work partnerships to ensure devices are appropriately represented in the Critical Path program.

Also, we would note that it could be misleading to see these as narrow categories of projects. The List is divided into six priority areas, rather than into product types, because these priorities—and many of these projects—apply across product areas and will require collaboration among experts in the development of drugs, devices, and biologics in order to succeed. For example, work to improve clinical trial design or to develop a robust clinical bioinformatics infrastructure will improve development of all medical products. Similarly, the full potential of genomic biomarkers to usher in an era of personalized medicine cannot be achieved without new approaches, not only to development of the drug or biologic therapy, but also to development of the partner in vitro diagnostic device needed to identify the presence or absence of the biomarker in an individual.

RESPONSE TO QUESTIONS OF SENATOR ENSIGN BY ANDREW C. VON ESCHENBACH

Question 1. Plan B contains the same ingredient used in prescription birth control pills, only in the case of Plan B, each pill contains a higher dose and the product has a different dosing regimen. Given this, why should we allow the stronger drug, Plan B, to be made over the counter when birth control is not?

Answer 1. Although the dose of the progestin in Plan B (0.75 mg levonorgestrel per tablet or 1.5 mg per treatment) is higher than that in individual prescription birth control pills, Plan B is to be used only as emergency or back up contraception while birth control pills that contain both estrogen and progestin (0.1 to 0.15 mg levonorgestrel) are generally taken for 21 of every 28 days in a cyclic pattern.

A major consideration for requiring that combination oral contraceptives be prescription-only products is the risks associated with oral contraceptive products that contain an estrogen. Women who take traditional oral contraceptives, in contrast to women who use Plan B for emergency or back up contraception, are at an increased risk of developing serious and sometimes fatal venous or arterial blood clots. This increased risk is attributed primarily to the estrogen component of oral contraceptives when taken on a cyclic, chronic basis. A similar increased risk for serious blood clots has not been reported for users of Plan B.

Question 2. From a broad perspective, what changes in FDA regulation and policy do you believe are necessary in order to modernize and improve the drug development, manufacturing, and review process?

Answer 2. On March 16, 2004, in the document "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products," FDA released a report addressing the recent slowdown in innovative medical therapies submitted to the FDA for approval. The report described the urgent need to modernize the medical product development process—the Critical Path—to make product development more predictable and efficient. A key insight is that FDA, industry, and academia are stakeholders in helping to coordinate, develop and disseminate solutions to these scientific hurdles. FDA has demonstrated a commitment to designating topics for joint development and investment while preparing internally for these changes.

Efforts are in progress to require clinical study data be provided in electronic format and require the use of standard data structure, terminology and code sets. The goals of this initiative will be to improve the efficiency of evaluation of the safety and efficacy of investigational treatments, enhance communication between the Agency and applicants, facilitate development of a more efficient review environment (e.g., access to data, orientation, redundancy, training, analysis tools), improve efficiency for clinical research, facilitate design and conduct of clinical trials, and enhance communication between researchers and study sponsors.

FDA leadership is developing a series of concept papers and guidance documents in areas such as advanced clinical trial designs, building greater efficiency in late stage clinical research, predictive toxicology models, use of biomarkers in drug development, and adverse event data mining. Collectively, these documents will help articulate the pathway toward improvement of the drug development process.

The regulatory groundwork for pharmacogenomics in the Critical Path is well underway. A final guidance on voluntary submissions of pharmacogenomic data has been issued and a concept paper on how to co-develop a drug or biological therapy along with a device test in a scientifically robust and efficient way has been created. The CDRH/CDER Draft Guidance for Industry and FDA Staff: Pharmacogenetic Tests and Genetic Tests for Heritable Markers was issued on February 9, 2006. This

draft guidance document is intended to facilitate progress in the field of pharmacogenomics and genetics by helping to shorten development and review timelines, facilitate rapid transfer of new technology from the research bench to the clinical diagnostic laboratory, and encourage informed use of pharmacogenomic and genetic diagnostic devices. As part of the cGMP Initiative of the 21st Century, CDER continues to make significant changes to our regulatory policies and the drug review process.

FDA will now be using a quality systems approach to improve the predictability, consistency, integration, and overall effectiveness of our entire regulatory operation. This quality systems model, now incorporated into the FDA Staff Manual Guide, Quality Systems Framework for Internal Activities, defines the essential quality elements to consider as part of any system that controls an internal FDA regulatory activity.

The Agency has released a draft guidance (Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations) describing how industry can implement quality management systems and risk management principles into the manufacture of pharmaceuticals.

CDER has developed and is implementing a new risk-based pharmaceutical quality assessment system to replace its current CMC review process. This new system should reduce the need to submit manufacturing supplements and increase first-cycle approval of new drug applications, thereby making drug products available to patients in a timelier manner. The system should also encourage manufacturers to implement new technologies, such as process analytical technology, and facilitate continuous manufacturing improvements.

FDA has revised its regulatory procedures for determining when to issue warning letters in response to noncompliance with CGMP requirements. All proposals to issue warning letters to human and animal drug and medicated feed manufacturers are reviewed by, among others, the centers with product jurisdiction. The Centers' continued role in the process will ensure that adverse findings will be based on the best science available. We are enhancing communication and coordination between the field and Centers with the goal of identifying possible program inconsistencies that can be resolved before a warning letter is issued.

At this time we believe that most of the necessary changes can be implemented without changing the regulations, however, as we move forward, we may find that regulatory changes may help in the implementation process. Currently, there is only one change in the regulations that we are working on to facilitate modernization of drug regulatory process; that is the regulation that covers how to report manufacturing changes and other changes to an approved marketing application (i.e., 21 CFR 314.70). The current regulation is more prescriptive and not flexible enough to allow manufacturers to efficiently implement innovative technologies into their pharmaceutical manufacturing plants.

Question 3. Do you believe that there are areas in which the FDA can improve the transparency of some of its regulatory decisions, particularly in how it addresses post-market drug safety issues? If so, what types of improvements should be made?

Answer 3. In the last 2 years, FDA has made a concerted effort to be more transparent about post-market drug safety issues by providing to health care professionals and the public timely information about new and emerging important drug risks. Since 2005, FDA has posted important new drug risk information on its Internet site, at: *http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm*. This site contains information sheets for healthcare professionals and for patients.

Healthcare Professional Sheets provide a brief description of the specific safety issue and recommendations or considerations (such as special monitoring or limiting use to specific patients) for the practitioner who is prescribing the drug. These sheets also summarize the data or other information that was the basis of the alert.

Patient Information Sheets provide a brief summary of the essential information about a specific drug in plain language. When there is an emerging safety concern for the drug, this concern will be summarized on the patient information sheet, along with the other information about the drug.

These information sheets are widely disseminated through the FDA MedWatch list serve program, which reaches more than 65,000 contacts. FDA is continuously evaluating this new program to identify ways to improve it.

In 2005 and 2006, the FDA began a series of other efforts to improve internal processes for identifying and resolving new safety concerns about specific drugs, such as establishing regular meetings to review the status of post-marketing drug safety concerns and establishing a system for tracking emerging concerns. For more information about the many advances FDA is making in this area, please visit: *http://www.fda.gov/cder/drugSafety.htm.*

Question 4. There is some debate about having the FDA collect data related to cost, cost-effectiveness, value, and other reimbursement considerations in order to address concerns with the Centers for Medicare and Medicaid Services coverage process. As you know, these are responsibilities that are outside of the current scope of FDA review.

Answer 4. I concur that these are the prerogatives of CMS, and I look forward to our close collaborations in support of our respective missions. Please see the answers to questions 5 and 6 for specific information on how FDA and CMS work together.

Question 5. Do you believe that FDA and CMS have distinct regulatory missions and that any harmonization of their responsibilities should be approached carefully?

Answer 5. Yes, FDA and CMS have distinct regulatory missions. However, the agencies share similar broad goals for enhancing the effectiveness of the health care system and work together productively and appropriately to further our respective missions. An excellent example of FDA-CMS collaboration is our recent effort to use certain CMS data to enhance FDA's computerized Adverse Event Reporting System.

Question 6. How can the FDA and CMS work together to speed access of safe and effective medical technologies for Medicare beneficiaries without delaying access to those same technologies by the rest of the American public?

Answer 6. By working together, FDA and CMS can enhance the speed in which Medicare beneficiaries, as well as the American public, gain access to safe and effective medical technologies. For example, industry is encouraged to work with both FDA and CMS simultaneously when seeking approval for marketing and Medicare national coverage. Working with both agencies at the same time can reduce the time it takes for specific medical technologies to be made available to the American public and to reduce the time it takes for a Medicare coverage decision.

Question 7. Given that the Medicare program and the Veterans Administration reimburse for compounded medicines, that virtually every hospital compounds medicines, and that our Armed Forces use compounded medications and require their pharmacists to be versed in compounding, would you agree that this demonstrates pharmacy compounding is a unique, legal and very valuable healthcare practice?

Answer 7. FDA has long recognized the important benefits of traditional pharmacy compounding. FDA regards traditional pharmacy compounding as the combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized medical needs of an individual patient. Traditional compounding enables a physician to prescribe, and a pharmacist to prepare, medication tailored to the needs of an individual patient, such as medication for a patient who is allergic to an ingredient in a commercially available drug, or diluted dosages for children.

Because of the benefits of traditional compounding, FDA exercises its enforcement discretion toward some kinds of compounding. FDA's willingness to exercise enforcement discretion does not change the fact that, under the Federal Food, Drug, and Cosmetic Act, compounded drugs are "new drugs" that require FDA approval before they may be marketed. When a pharmacist compounds a drug, by definition, he or she creates a new drug under Federal law because the compounded product is not "generally recognized among experts . . . as safe and effective." The fact that these drugs are produced in a pharmacy does not exempt them from the new drug definition.

Traditional pharmacy compounding serves an important public health function by meeting the specialized medical needs of individual patients for whom commercially available approved drugs are inadequate or inappropriate. FDA has directed its enforcement actions toward establishments that manufacture, under the guise of compounding, large quantities of unapproved new drugs that are commercial copies of approved drugs, or whose compounding practices pose a significant or immediate threat to the public health or to the integrity of the drug approval processes of the FDA.

FDA's current enforcement policy with respect to pharmacy compounding is articulated in Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"] (May 2002), which is available on FDA's Internet site at: *www.fda.gov/cder/pharmcomp/default.htm*. The CPG lists factors that the Agency considers in deciding whether to exercise its enforcement discretion with respect to pharmacy compounding. The factors in the CPG are not intended to be exhaustive and other factors may also be appropriate for FDA's consideration.

FDA has seen abuses, such as large-scale drug manufacturing under the guise of pharmacy compounding, compounding drugs that are essentially copies of commercially available FDA-approved products or that were withdrawn or removed from

the market for safety reasons, and compounding products containing active ingredients that are not components of FDA-approved drugs. In some cases, FDA has reason to be concerned about the quality of the drugs being compounded and the potential risks to patients who may take them. Some compounding pharmacies may lack sufficient controls to ensure product quality or to compound difficult products such as sterile or modified release drugs. Additionally, compounding that is done on a large scale and is not done properly can expose large numbers of patients to health risks associated with unsafe or ineffective medications.

Question 8. The Washington Post recently reported that more than one-fifth of all prescriptions for approved drugs are used for off-label use, which means for uses that, like compounded medicines, are not subject to FDA approval requirements for safety and efficacy. Would you agree that it is important to protect the right of physicians to prescribe such treatments for their patients?

Answer 8. Once a drug is approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not listed in the FDA-approved labeling. FDA does not generally interfere with the practice of medicine, such as the decision by a physician to prescribe a legally marketed medication for their patient for an indication not listed on the drug's label. Physicians under their own responsibility may exercise judgment for the use of an approved drug for unlabeled indications when they are satisfied there is medical and scientific support that such use may benefit their patients.

Question 9. Are all compounded medications new drugs, and does every new compounded prescription need to go through a drug approval process?

Answer 9. All compounded prescription drugs are "new drugs" within the meaning of the Federal Food, Drug, and Cosmetic Act (FDCA). When a pharmacist compounds a prescription drug, by definition, he or she creates a new drug under Federal law because the compounded product is not "generally recognized among experts . . . as safe and effective." The fact that these drugs are produced in a pharmacy does not exempt them from the new drug definition.

Under the FDCA, a "new drug" (including a compounded new drug) may not be legally introduced, or delivered for introduction into interstate commerce in the United States unless it has been pre-approved by FDA as safe and effective for its intended uses. Traditional compounding typically is used to prepare medications that are not commercially available; it involves providing a service in response to a physician's prescription to accommodate the specialized medical needs of a particular patient. In virtually every instance, the drugs that pharmacists compound have not been so approved. FDA, as a matter of policy, historically has not brought enforcement actions against traditional forms of pharmacy compounding.

FDA has directed its enforcement actions toward establishments that manufacture, under the guise of compounding, large quantities of unapproved new drugs that are commercial copies of approved drugs, or whose compounding practices pose a significant or immediate threat to the public health or to the integrity of the drug approval processes of the FDA.

Question 10. According to a recent Institute of Medicine Study, at least 1.5 million Americans are sickened, injured, or killed each year by errors in prescribing, dispensing, and taking medications. Does the FDA receive reports that suggest that medication errors occur and that such errors may contribute to adverse health outcomes? Could e-prescribing help solve these problems? What do you plan to do to advance the Agency's drive to reduce medication errors?

Answer 10. The Food and Drug Administration has been receiving reports of medication errors since January 1992. Although there is no requirement to submit reports of medication errors to FDA, we receive over 5,000 reports yearly, primarily from health care professionals and consumers.

Medication errors occur due to numerous contributing factors at any point in the medication use process (e.g., procurement, prescribing, preparing/dispensing, administering and monitoring). Patient outcomes may vary from "no harm" to "death," depending on the drugs involved and the nature of the event.

The Agency's approach to medication error prevention includes the review of proposed brand names along with labels, labeling and packaging for drugs and biologics to minimize the potential for errors. After approval we evaluate, monitor, and take appropriate action based on reports of medication errors. We educate and provide feedback to health professionals and share information with outside organizations involved in preventing medication errors.

E-Prescribing or Computerized Physician Order Entry (CPOE) has been found to improve drug safety. However, CPOE will not in itself solve all medication errors. CPOE will have a greater impact on errors that result from misinterpretations of

prescriber handwriting or misinterpretations of incomplete or ambiguous drug orders, and it affords a number of checks for health care providers about a patient's drug allergies, possible drug interactions, higher-than-recommended doses, and drug-laboratory problems.

In 2004, the Food and Drug Administration (FDA) issued a new rule to require certain human drug and biological product labels to have bar codes. The bar code for human drug products and biological products (other than blood, blood components, and devices regulated by the Center for Biologics Evaluation and Research) must contain the National Drug Code (NDC) number in a linear bar code. The rule will help reduce the number of medication errors in hospitals and other health care settings by allowing health care professionals to use bar code scanning equipment to verify that the right drug (in the right dose and right route of administration) is being given to the right patient at the right time. The rule also requires the use of machine-readable information on blood and blood component container labels to help reduce medication errors.

On January 18, 2006 FDA issued the physician labeling rule which is the first major revision to the format of prescription drug information (package insert) in 25 years.

The revisions are a major public health advance in that they make it easier for healthcare professionals to access, read, and use prescribing information, and therefore, will enhance the safe and effective use of prescription drug products.

Some of the most significant changes include:

- A new section called *Highlights* to provide immediate access to the most important information about risks and benefits.
- A *Table of Contents* for easy reference to detailed safety and efficacy information.
- The date of initial product approval, making it easier to determine how long a product has been on the market.
- A toll-free number and Internet reporting information for suspected adverse events to encourage more widespread reporting of suspected side effects.

The new prescription information format will be integrated into FDA's other e-Health initiatives and standards-setting efforts through a variety of ongoing initiatives. As prescription information is updated it will be used to provide medication information for DailyMed, a new interagency online health information clearinghouse that will provide the most up-to-date medication information free to consumers, healthcare professionals and healthcare information providers. In the future, this new information will also be provided through a Website called facts@fda, a comprehensive Internet resource designed to give one-stop access for information about all FDA-regulated products.

FDA is committed to working with other government agencies, professional and patient groups and industry to continue to reduce the incidence of medication errors through better consumer medical information, improved drug labeling and naming, and through an enhanced electronic health information architecture to ensure that safety information is communicated efficiently and effectively.

Question 11. In terms of drug safety, I am extremely concerned about the approval process for RU-486. At least three women in the United States have died using RU-486, which was approved under FDA's emergency "Subpart H," an approval process reserved only for drugs that treat "severe or life-threatening illnesses." Can you please explain the approval process for RU-486? How was this drug determined to be "safe and effective," and why was this drug approved under an accelerated review process, and why is this drug still accessible?

Answer 11. I strongly support women's health issues and ensuring that the medical products FDA regulates are safe and effective for consumers who use them. While I was not at FDA when Mifeprex was originally approved, I am committed to rigorous post-approval adverse event reporting. The Agency takes all adverse event reports seriously, and we are especially concerned with reports of deaths of otherwise healthy women potentially associated with use of a FDA-approved drug. We are monitoring this situation closely.

FDA's review and approval of the Mifeprex application complied with the Federal Food, Drug, and Cosmetic (FD&C) Act and FDA regulations, including the requirements under section 505(d) of the FD&C Act that (1) there be adequate tests to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the approved labeling (section 505(d)(1)) and (2) there be substantial evidence that the drug will have the effect it purports or is recommended to have under the conditions of use prescribed, recommended, or suggested in the labeling (section 505(d)(5)). Section 505(d) defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investiga-

tions, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved . . ."

FDA's approval of the Mifeprex application on September 28, 2000, was based on three "adequate and well-controlled" studies as that term is defined in Title 21, Code of Federal Regulations (CFR) section 314.126, applicable to new drug applications (NDAs) under 505(b) of the FD&C Act. The Mifeprex NDA contained data from three clinical trials (a large U.S. trial and two French trials) and safety data from a post-marketing database of over 620,000 women in Europe who had had a medical termination of pregnancy (approximately 415,000 of whom had received the combination regimen of mifepristone together with the drug misoprostol). These data constituted evidence that mifepristone was safe and effective for its approved indication, the medical termination of intrauterine pregnancy through 49 days' pregnancy, in accordance with section 505(d) of the FD&C Act. Previously, FDA's Reproductive Health Drugs Advisory Committee voted 6 to 0 (with two abstentions) on July 19, 1996, that the benefits of mifepristone exceeded the risks of the product.

The Mifeprex application was approved under FDA's Subpart H regulations (21 CFR part 314 Subpart H). FDA approved the Mifeprex NDA under Subpart H because the Agency determined that post-marketing distribution restrictions on the product were necessary to ensure its safe use. As FDA made clear in the preamble to the final rule adopting Subpart H, the Subpart H regulations are intended to apply to serious or life-threatening conditions as well as diseases. For example, the final rule cites depression and psychoses as "examples of conditions or diseases that can be serious for certain populations or in some or all of their phases" and that therefore drugs to treat them 'could be covered by the' regulations." (57 FR 58942 at 58946, Dec. 11, 1992).

Under § 314.520 of FDA's regulations, if FDA concludes that a drug product shown to be effective can be used safely only if distribution or use is restricted, the Agency will require post-marketing restrictions. As part of the Subpart H approval for Mifeprex, distribution of the drug was restricted in several ways, including that it must be provided by or under the supervision of a physician who meets several qualifications. Approval under this regulation does not imply that the review was "accelerated" by virtue of reliance on a surrogate endpoint, but rather that FDA had concluded that Mifeprex had been shown to be effective, but could be used safely only if distribution or use was restricted.

FDA has been following and evaluating safety concerns about mifepristone since its approval. As a result of this ongoing monitoring of safety issues, FDA has approved two revisions to the Mifeprex drug labeling and Medication Guide, in November 2004 and in July 2005. In November 2004, the boxed warning was revised and strengthened to add new information on the risk of serious bacterial infections, sepsis, bleeding, and death that may occur following any termination of pregnancy, including use of Mifeprex. In July 2005, FDA approved a labeling supplement to again strengthen the boxed warning on the product by noting that "atypical presentations of serious infection . . . can occur without fever, bacteria or significant findings on pelvic exam . . ." and to advise patients to seek immediate medical attention if they experience prolonged heavy bleeding. Additionally, FDA has issued several Public Health Advisories and updated the Mifeprex webpage on the Agency's Website several times to reflect new safety information. The sponsor has issued several Dear Healthcare Professional letters and a Dear Emergency Room Director letter, and two MedWatch alerts have been issued.

The deaths that have occurred in the United States in association with the use of mifepristone for termination of pregnancy continue to be of concern to the Agency. Most of the deaths have been caused by severe infection, or sepsis, primarily with a specific bacterium, *Clostridium sordellii*. These cases of severe infection occurred with regimens of mifepristone and misoprostol that were not in approved labeling, although the relationship of the infections to the use of mifepristone and misoprostol remains unknown. In a recent workshop, "Emerging Clostridial Diseases," held Thursday, May 11, 2006, in Atlanta, Georgia, cases of infection due to *Clostridium sordellii* were also identified in women with ongoing pregnancies and delivery and in women who had recently experienced spontaneous miscarriages. There appeared to be broad consensus at the workshop that additional research is necessary to improve our clinical understanding of *Clostridial* infections associated with pregnancy, labor and delivery, and termination of pregnancy. FDA is committed to continuing to work with other Federal agencies to develop more information on *Clostridial* diseases.

Question 12. Biotech drugs can cost between $10,000 and $20,000 a year per patient. As a result, few patients can afford these new drugs, and even when some insurers cover their costs, they constitute an unsustainable and growing burden on

Medicare, Medicaid, and the healthcare system in general. Other countries, including the European Union have already approved a general regulatory pathway or the approval of generic or follow-on biologics.

Over the past few years, the FDA has held a number of advisory committee and public hearings on the issue of generic or "follow-on" biologics. I understand that the Agency may have even developed some draft guidance documents. Do you know if the FDA intends to release any guidance on this issue any time in the near future?

Answer 12. For biologic products approved under section 505 of the Food, Drug, and Cosmetic (FD&C) Act, we believe there is existing authority to allow applications for generic or follow-on protein products to be approved under sections 505(b)(2) or 505(j) of the FD&C Act where scientifically appropriate. Numerous protein products, however, are licensed as biological products under section 351 of the Public Health Service (PHS) Act, and are not approved as drugs under the FD&C Act. There is no abbreviated approval pathway for protein products licensed under section 351 of the PHS Act analogous to sections 505(b)(2) or 505(j) of the FD&C Act for drugs. Such a pathway for the approval or licensure of follow-on protein products under the PHS Act would require new legislation.

Please be assured that FDA's consideration of regulatory requirements for follow-on protein products is progressing. FDA has sought input from stakeholders and conducted an extensive public discussion on scientific issues relating to the development and approval of follow-on protein products, including two public meetings (September 2004 and February 2005) and a co-sponsored workshop (December 2005). The public meetings resulted in a large number of comments and concerns from interested parties that are being considered further as we develop policies for regulating follow-on protein products. FDA recognizes that guidance for industry would be helpful, and intends to publish guidance broadly applicable to follow-on protein products in a timely manner. FDA expects that this approach will provide useful guidance to the industry, while ensuring that we do not stifle innovation and the utilization of state-of-the-art technologies. In addition, a sponsor may contact the Agency to request advice on a case-specific basis regarding the development of a follow-on protein product for submission in an application under section 505 of the FD&C Act.

I do want you to know, however, that even as guidance documents on follow-on protein products are being developed, the Agency has been moving forward with the review and approval of those follow-on protein products for which the sponsors have met the statutory and regulatory approval requirements under section 505. Most recently, we have approved Fortical (calcitonin salmon recombinant) Nasal Spray in August 2005, Hylenex (hyaluronidase recombinant human) in December 2005, and Omnitrope (somatropin [rDNA origin]) in May 2006.

Question 13. As you know, the prescription drug user fee program has been tremendously successful in strengthening the FDA's resources and ensuring the timely review of new treatments. Do you think that such a user fee program could successfully be extended to the review of generic drugs?

Answer 13. As you may know, the Prescription Drug User Fee Act does not apply to generic drugs approved under the ANDA process, section 505(j) of the Federal Food, Drug, and Cosmetic Act. We have heard public discussion of a generic drug user fee program, but at this time, the Administration has no position on such proposals.

Question 14. As you know, human papillomavirus (HPV) is the cause of nearly all cervical cancer. In 1999, the National Cancer Institute reported to Congress that "Condoms are ineffective against HPV" and that "additional research efforts by NCI on the effectiveness of condoms in preventing HPV transmission are not warranted." In 2000, President Clinton signed Public Law 106–554, which directs the FDA to re-examine condom labeling to ensure that such labels are medically accurate regarding the lack of effectiveness of condoms in preventing HPV infection. It has been 5½ years since this law was signed and this label change has still not occurred. Millions of Americans have become infected with HPV during that time. Will you ensure that FDA will enforce this law by the end of this year?

Answer 14. Public Law No. 106–554 directed FDA to re-examine existing condom labels and determine whether the labels are medically accurate regarding the overall effectiveness or lack of effectiveness of condoms in preventing STDs, including HPV. The Agency undertook a rigorous review of available scientific information and re-examination of condom labeling, which reaffirmed that latex condoms reduce the risk of HIV/AIDS and many STD's. However, FDA further concluded the degree of risk reduction varies for different types of STD's. Specifically, the Agency found

that condoms provide less protection for certain STDs, including HPV, that can be spread by contact with infected skin outside the area covered by the condom. FDA also found that using a condom may lower the risk of developing HPV-related diseases, such as genital warts and cervical cancer. In November 2005, we published a proposed rule and draft special control guidance document with recommended new condom labeling language to communicate this nuanced public health message. FDA received roughly 400 comments on the proposed rule. Almost all comments suggested the proposed labeling language was confusing and difficult for consumers to understand. As a result, the Agency intends to undertake additional labeling comprehension studies to help ensure that the final labeling recommendations issued by the Agency are understandable to users. We remain committed to providing the American people the best possible information and believe ensuring the labeling's understandability to users is a critical component in providing this information.

RESPONSE TO QUESTIONS OF SENATOR HATCH BY ANDREW C. VON ESCHENBACH

Question 1. Please provide a copy of the guidance, or if it was not finalized, the last draft, governing follow-on approvals of human growth hormone and insulin or any other biological products.

Answer 1. The Agency has reconsidered issuing at this time the draft guidance documents on human growth hormone and insulin you reference for a number of reasons. After re-assessing these "product-specific" draft documents, FDA has decided that it would be more appropriate to initially publish guidances that are more broadly applicable to follow-on protein products in general. FDA expects that this approach will provide useful guidance to the industry, while ensuring that we do not stifle innovation and the utilization of state-of-the-art technologies. In addition, a sponsor may contact the Agency to request advice on a case-specific basis regarding the development of a follow-on protein product for submission in an application under section 505 of the FD&C Act.

With regard to your request for the Agency's preliminary draft guidance documents on human growth hormone and insulin, I note that these internal draft documents were never finalized and were not cleared by Center for Drug Evaluation and Research (CDER) management, thus they do not necessarily reflect CDER's current thinking on these topics. For this reason, we would not disseminate these deliberative documents outside FDA.

I do want you to know, however, that even as guidance documents on follow-on protein products are being developed, the Agency has been moving forward with the review and approval of those follow-on protein products for which the sponsors have met the statutory and regulatory approval requirements under section 505. Most recently, we have approved Fortical (calcitonin salmon recombinant) Nasal Spray in August 2005, Hylenex (hyaluronidase recombinant human) in December 2005, and Omnitrope (somatropin [rDNA origin]) in May 2006.

Question 2. Dr. von Eschenbach, along with Senator Harkin, I have been imploring the Administration to issue the Good Manufacturing Practice guidelines for dietary supplements that were authorized in 1994. I believe the cGMPs for supplements were finalized during the Clinton administration, but never published. Despite our entreaties, correspondence, and language in two Senate Appropriations Committee reports, these guidelines have not been published.

Could you please tell me, specifically, what issues are remaining that preclude issuing this rule?

If you cannot tell me the issues, could you please tell me whom in the Administration I should contact to further my discussion?

Answer 2. FDA is committed to publishing this final rule. I can assure you that there has been significant work done on the final rule since the comment period for the proposed rule ended in August 2003.

Since we are still in the rulemaking process, I can not tell you what specific issues are being discussed, but I can tell you that the issues have been complex, legally and substantively, and in some cases, novel. The final rule is currently under review by the Office of Management and Budget.

We have expended significant internal resources on reviewing and preparing responses to the comments received. We also have worked extremely hard to draft the final rule in order to assure quality products for the consumer while minimizing the economic impact to the dietary supplement industry. I can assure you that full attention is being given to the completion of the rule as soon as possible.

Question 3. Has the FDA considered, or will you consider, issuing this rule in a way that allows for public comment, given that the rule has been several years in development? It seems that the proposed rule and the final could differ substantially

given the time lag and it seems only fair to allow those who must abide by these regulations to be able to comment on its latest iteration.

Answer 3. In the past, we have had rules issued in which there has been a similar period of time between the end of the comment period and publication of the final rule. We are confident that the final rule will address all of the issues raised by comments. If we determine there is any need for additional public comment, we will consider the appropriate means to address that need.

Question 4. The HELP Committee has before it S. 3128, the National Uniformity for Food Act, which establishes a national food labeling standard. The bill contains a provision which allows States to petition FDA for an exemption from national uniformity in order to address a local problem. There is also a provision whereby States may petition for a State standard that differs from requirement imposed throughout the rest of the country.

Could you please tell the committee the resources FDA expects it would take to implement these two provisions? In particular, I would be interested to learn how many FTEs would be needed and at what cost? Further, in each of the two cases, I would be interested to learn how long the Agency estimates it would take to act on a petition it receives? If the answer is qualified according to how complicated the petition might be, I would appreciate your providing me with a time range for action. Finally, if this bill is enacted, would your action on petitions be contingent on an appropriation?

Answer 4. FDA does not have cost estimates of the impact of S. 3128.

Question 5. Will you commit to having an open dialogue with the Congress and with the dietary supplement industry on issues relating to the science and regulation of dietary supplements? Do you believe the Dietary Supplement Health and Education Act is adequate to deal with any problems which may arise connected with dietary supplements?

Answer 5. I look forward to open communication with Congress and the dietary supplement industry on issues relating to the science and regulation of dietary supplements.

With regard to your second question, the Dietary Supplement Health and Education Act of 1994, or DSHEA, provides FDA the authority to act against dietary supplements that carry unsubstantiated claims or claim to treat a disease, that are unsafe, or that are otherwise adulterated or misbranded.

DSHEA created a regulatory framework that is primarily postmarket in nature. FDA's responsibilities under this framework include implementing DSHEA's requirements for dietary supplement safety, labeling, and product quality, as well as taking action against adulterated and misbranded products. Since the enactment of DSHEA, FDA has promulgated a number of implementing regulations and begun other regulatory actions. The challenge to FDA is to strike the right balance between preserving consumers' access to products and information and ensuring the safety and proper labeling of these products. Under DSHEA, the primary responsibility for producing and marketing dietary supplements that are safe, accurately labeled, and appropriately promoted rests with the manufacturer. Although the law requires a firm to possess substantiation that claims made for its products are truthful and not misleading, there is no current requirement for the firm to submit that information to FDA or publicly disclose it. Nor do dietary supplement firms have to submit safety data on their products, except in the case of supplements that contain certain new dietary ingredients. The burden of proving a product is unsafe rests with FDA.

On August 17, 2006, the U.S. Court of Appeals for the Tenth Circuit in Denver upheld FDA's final rule declaring all dietary supplements containing ephedrine alkaloids adulterated, and therefore illegal for marketing in the United States, reversing a decision by the U.S. District Court for the District of Utah. The Tenth Circuit Court of Appeals' ruling demonstrates the soundness of FDA's decision to ban dietary supplements containing ephedrine alkaloids, consistent with DSHEA.

On November 4, 2004, FDA published a Regulatory Strategy for the Further Implementation and Enforcement of DSHEA, in which FDA detailed specific steps for the further implementation of DSHEA. This Regulatory Strategy identified three specific initiatives: (1) monitoring and evaluating product and ingredient safety, (2) assuring product quality through CGMP regulations, and (3) monitoring and evaluating product labeling. With this strategy, FDA intends to improve the transparency, predictability, and consistency both of the Agency's scientific evaluations of dietary supplement product and ingredient safety, and of its regulatory actions to protect consumers against unsafe dietary supplements and dietary supplements making unauthorized, false, or misleading claims, including unsubstantiated claims.

FDA expects that this improved transparency will help engage stakeholders in the development of further measures to implement DSHEA. The Agency believes that its regulatory strategy will give consumers a higher level of assurance of product quality and safety.

Question 6. I am aware that Mr. Jeffrey A. Hinrichs, Chief Operating Officer of Nutraceutical in Park City, Utah, sent a June 13, 2006 letter to Mr. Michael M. Landa, Deputy Director for Regulatory Affairs (CFSAN), about the effect on public health of your pesticide residue testing program for ginseng. I would appreciate your view of the response to Mr. Hinrichs' letter, and your making the reply available for this record.

Answer 6. Nutraceuticals wrote to the Deputy Director for Regulatory Affairs, Michael Landa, June 13, 2006, regarding the effects of FDA's Pesticide Residue Testing Program for Gingseng on public health. Nutraceuticals maintains that there is no evidence that pesticides like the Quintozene and Procymidone residues found on gingseng have ever created, or are likely to create, any public health concern.

FDA's position remains that its pesticide residue monitoring program is fully consistent with the law. As we have consistently found ginseng to be contaminated with a variety of illegal pesticide residues, it is appropriate for FDA to continue to monitor these products for pesticide residues.

In lieu of responding in writing, FDA is in the process of scheduling a meeting with Nutraceuticals, as the company requested, to discuss the issues it has raised.

RESPONSE TO QUESTIONS OF SENATOR SESSIONS BY ANDREW C. VON ESCHENBACH

Question 1. What exactly is Plan B?

Answer 1. Plan B is a drug intended to prevent pregnancy after unprotected sex (if a barrier contraceptive fails or if no contraception was used). It contains levonorgestrel (0.75 mg per tablet), which is a synthetic hormone (progestin) commonly used in birth control pills. Plan B is for emergency use, and should not be used in place of regular contraception.

Question 2. How is it to be administered?

Answer 2. The woman should take the first Plan B tablet as soon as possible within 72 hours of unprotected sex. She should take the second tablet 12 hours after taking the first tablet. Plan B is more effective the sooner treatment is started following unprotected sex.

Question 3. What are the possible side effects of Plan B and how are they different from regular birth control pills?

Answer 3. The most common side effect related to the use of Plan B is a change in the timing and/or amount of bleeding related to the user's next menstrual period, which may occur earlier or later than expected. Menstrual bleeding is sometimes heavier and sometimes lighter than usual after women take Plan B. After taking Plan B most women get their next period within 1 week of when it is expected. Other adverse events that have been reported in women using Plan B in clinical trials have included nausea, abdominal pain, fatigue, headache, dizziness, breast tenderness, vomiting, and diarrhea. It is not known if these events were directly related to the use of Plan B since these events are not uncommon in women who do not use Plan B.

All of the adverse events that have been reported in users of Plan B have been reported in users of oral contraceptives that contain both estrogen and a progestin. However, users of oral contraceptives that contain estrogen have an increased risk of developing serious and sometimes fatal venous or arterial blood clots. A similar increased risk for serious blood clots has not been reported for users of Plan B.

Question 4. Currently, regular birth control pills can only be obtained with a prescription. Why? Are there possible side effects that could be harmful to a woman's health?

Answer 4. Users of oral contraceptives have an increased risk of developing serious and sometimes fatal venous or arterial blood clots. A similar increased risk for serious blood clots has not been reported for users of Plan B. Because of the seriousness of this risk associated with the use of traditional oral contraceptives, women who use oral contraceptives must be carefully screened by a physician to ensure that they do not have any of the contraindications to the use of oral contraceptives that would increase their risk of developing serious adverse events. Users of oral contraceptives also need to have regular periodic medical examinations because

long-term use of oral contraceptives may increase blood pressure, alter blood lipids levels, and decrease carbohydrate metabolism in some women.

Question 5. Considering the side effects of and prescription requirement for traditional birth control, why does the FDA consider Plan B safe enough to be available over-the-counter? Is Plan B a stronger dose of medication than traditional birth control?

Answer 5. Although the dose of the progestin in Plan B (0.75 mg levonorgestrel per tablet or 1.5 mg per treatment) is higher than that in individual prescription birth control pills, Plan B is to be used only as emergency or back up contraception while birth control pills that contain both estrogen and progestin (0.1 to 0.15 mg levonorgestrel) are generally taken for 21 of every 28 days in a cyclic pattern. The major consideration for requiring that combination oral contraceptives be prescription-only products is the risks associated with the estrogen component of the product. The estrogen component of oral contraceptives is thought to be responsible for the increased risk of serious blood clots as mentioned earlier. A similar increased risk for serious blood clots has not been reported for users of Plan B. In addition, users of oral contraceptives may develop other adverse changes (e.g., increased blood pressure) that require periodic physical examinations to detect.

Question 6. Have there been any cases of women who have taken it incorrectly and experienced harm? I have heard stories of women who take Plan B regularly, as a substitute for birth control pills. Is this harmful, and if so, how can we prevent it from happening—especially if Plan B becomes an over-the-counter drug?

Answer 6. We are not aware of any cases where a woman has taken Plan B incorrectly and experienced harm. It is possible that some woman may use prescription Plan B as a substitute for oral contraceptives; however, there is no evidence to indicate this is a consumer practice. If Plan B is available for women 18 years and older without a prescription, we believe that regular use of Plan B as an alternative for birth control pills will continue to be very uncommon. The basis for our belief includes: (1) our understanding that a single treatment (two pills) of Plan B will be more costly than a month's supply of most oral contraceptives and (2) the labeling for non-prescription Plan B will include: (a) a warning against its use as a regular birth control method and (b) a statement that Plan B does not work as well as most other forms of birth control when they are used consistently and correctly. The distributor of Plan B will also promote its correct use in advertising.

ADDITIONAL QUESTIONS OF SENATOR SESSIONS FOR ANDREW C. VON ESCHENBACH

Question 1. I am very concerned about the drug RU–486. Has anyone actually died as a result of taking this much-discussed drug? Please share a complete list of drugs that have remained on the market after deaths have occurred in relation with them.

Question 2. How does RU–486 work and what is the drug's level of effectiveness in carrying out its intended effect, which is the termination of pregnancy?

Question 3. I hear that RU–486 is 10 to 14 times more lethal to the mother than surgical abortion during the first 49 weeks of gestation when RU–486 is used. Is this true? How lethal is RU–486 to women in comparison to a surgical abortion?

Question 4. In my home State of Alabama, a clinic was recently closed after a terrible incident. A woman went into an abortion clinic where a staff member performed an ultrasound and determined she was 6 weeks pregnant—in truth she was nearly full term. At that point, the nurse practitioner, rather than the doctor, administered the drug even though the woman's blood pressure was dangerously high. I must note that a doctor was not present during any of these medical procedures, including the administering of RU–486. Six days later, the woman went to a hospital emergency room with the baby's head protruding and delivered a stillborn 6-pound, four-ounce baby. This is not an isolated story, and in fact it is a story with a much happier ending than those women who have actually died as a result of taking RU–486. I find it shocking that this drug is still on the market. If you are confirmed and officially appointed FDA Commissioner, what will you do about this? What are your intentions insofar as monitoring, warning, and promptly removing dangerous drugs?

Question 5. As you know, Vioxx and other drugs have been pulled, many of which have shown to be less dangerous than RU–486. There is even talk of new drug safety legislation in this very committee. What, if any, legislative changes need to take

place to empower the FDA to do its job in protecting the American people and ensuring that drugs are safe before they go on the market, as well as pulling drugs that show to be dangerous in a timely manner?

Question 6. RU–486 is a drug that requires precise timing and cannot be taken after a woman reaches her seventh week of pregnancy. Do you have any confirmed reports of RU–486 being taken past the 49th day of pregnancy? If so, who prescribed the drugs (i.e., clinic, a physician's office)?

Question 7. I understand that RU–486 was approved in September 2000 through the seldom-used, accelerated process called Subpart H (used to accelerate drugs needed for "serious or life-threatening illnesses"). What other drugs were approved through this process and what illnesses were they intended to cure? What serious or life threatening illness was Mifeprex (the RU–486 drug) intended to treat? Have any other drugs been approved to treat this or related serious or life-threatening illnesses since 1992? Were any of these drugs approved pursuant to Subpart H, which was previously reserved?

Question 8. Aside from Mifeprex, in the past 20 years how many new drug applications has FDA approved based solely on data from clinical trials with only a treatment art (i.e., lacking a control group)? How many of these approvals took place after Subpart H was enacted in 1992? Of the approvals since 1992, how many were approved under Subpart H?

Question 9. In the past 20 years how many new drug applications has FDA approved based solely on data from historically controlled trials? For each answer provide the name of any drugs, and a brief description of the trials, including the control group used.

Question 10. Which drugs approved prior to 1992 have restrictions placed on their distribution and use? Which drugs approved since 1992 have had restrictions placed on their distribution and use under Subpart H? Which drugs approved since 1992 have had restrictions placed on their distribution and use but were not approved under Subpart H? How many drugs approved under Subpart H have been removed from the market for safety or effectiveness concerns? For these questions, please list the applicable drug name(s) and approval date(s).

Question 11. What procedures are in place to evaluate and assess the adequacy of the restrictions on the distribution and use of Mifeprex and the applicant's adherence to them? Which drugs with restrictions placed on their distribution and use under Subpart H have been removed from the market for noncompliance with those restrictions? Which drugs with restrictions placed on their distribution and use under Subpart H were given additional restrictions on distribution due to noncompliance with those restrictions? For these questions, please list the applicable drug name(s) and date of removal from the market or date of approval of additional restrictions as applicable.

Question 12. Who owns Danco Laboratories, the producer of Mifeprex? Where is their business located, and what other drugs do they produce?

Question 13. What communication has the FDA had with Danco, and what type of communication do you intend to have if you are confirmed?

[Editors Note: The response to additional questions from Senator Sessions were not available at time of print.]

RESPONSE TO QUESTIONS OF SENATOR DODD BY ANDREW C. VON ESCHENBACH

Question 1. Events of the past few years have cast into doubt the FDA's ability to ensure that the drugs it approves are safe—especially once they are on the market. These concerns are bad for patients, bad for physicians, and bad for the drug industry. Patients have come to trust the words "FDA Approved," and those words have also become the gold standard around the world. But the FDA is and has been facing a crisis in confidence. A recent survey of 997 FDA scientists conducted by the Union of Concerned Scientists and the Public Employees for Environmental Responsibility, found that 378 scientists disagreed or strongly disagreed that the FDA is acting effectively to protect public health. In that survey, 420 scientists reported that they knew of cases in which the Department of Health and Human Services or FDA political appointees have inappropriately injected themselves into FDA determinations or actions.

Dr. von Eschenbach, during testimony before this committee earlier this month, you stated that drug safety is one of your top priorities. Should you be confirmed as Commissioner of the FDA, your most important task will be to restore confidence in the words "FDA Approved," so that patients can be sure that the drugs they take to help them will not harm them instead.

Please describe, in detail, the steps you would take as FDA Commissioner to restore public confidence in FDA.

Answer 1. I am committed to maintaining, and improving, the long-standing traditions and values of an Agency whose processes and decisions are guided by sound science and vigorous analysis of evidence and based on the best interests of the patients and public we serve.

This year, FDA celebrates 100 years of successes in becoming the world's gold standard for assuring the drugs we give our children, the medical devices we use to treat disease and the food we eat is safe and effective. The Agency's more than 12,000 employees remain fully dedicated to continuously improving and becoming even better as we enter our second century. FDA is as committed as ever to its time-honored tradition of encouraging vigorous debate among experts who use disciplined processes to arrive at consensus and conclusions.

Much work remains to fully equip FDA to face the challenges of the 21st Century and seize the opportunities ahead, but I am confident that we are on the right path. And if confirmed, I believe I can provide the leadership and management that will guide this important public health agency proudly and effectively into its second century of service.

TRANSPARENCY

Question 2a. Dr. von Eschenbach, the manufacturer of Ketek was enrolling children in clinical trials for its antibiotic since June 2005. Despite FDA knowledge of repeated instances of fraud in adult clinical trials sponsored by the company and warnings from Dr. Johann-Liang and others at FDA, pediatric clinical trials in children as young as 6 months of Ketek continued until June 2006.

Do you believe mistakes were made in FDA's handling of Ketek's approval process and post-market surveillance?

Answer 2a. The Ketek application was carefully reviewed and evaluated. There were two approvable letters issued and additional information submitted and reviewed prior to receiving FDA approval. The data from Study 3014 was eliminated as a basis for approval for Ketek and instead, the Agency relied on the post-marketing experience of approximately 4 million prescriptions for patients in foreign countries to conclude that the drug was safe for its intended use.

As part of the standard FDA post-marketing surveillance program, a 1-year post-approval assessment was performed (June 2005) and no safety concerns regarding liver toxicity where identified at that time.

As with any drug, Ketek labeling contains known adverse events that are described in the product labeling, however, after the 1-year post-approval assessment FDA was alerted to an increased rate of liver toxicity through the adverse event reporting system (AERS). FDA promptly initiated another safety assessment which was recently completed and provides support for the action that FDA took on June 29, 2006. This action provides new safety information in the Ketek product label, including a Warning regarding liver toxicity.

Question 2b. Do you think it is appropriate for the FDA to continue to cite studies later found to be fraudulent to support a drug's safety?

Answer 2b. No, it is not appropriate. As noted above, this data was eliminated from consideration with respect to the approval. The relevant information on FDA's web page for Ketek has been updated.

Question 3. As Commissioner of the FDA, what would you do to ensure transparency, so that dissenting opinions are seriously considered and never suppressed?

Answer 3. First, I will make myself available to staff who want to appeal decisions made by FDA management. I believe that the need to appeal to me will be rare, however, because I will ensure that there are strong policies and procedures in place for resolving issues involving dissenting opinions. Efforts toward that end will include promulgating new policies and procedures as necessary, and strengthening, by process improvement and best practices measures, many of those that are already in place.

For example, we are working to ensure a rigorous ombudsman program through which staff are welcome to promulgate dissenting opinions. Staff may also invoke standard written procedures for facilitating and resolving differing professional opinions. In addition, at the direction of the Secretary, FDA's Center for Drug Eval-

uation and Research established a Drug Safety Oversight Board whose charter includes responsibility for deliberating on any dissenting opinions raised during evaluation of drug applications and surveillance of marketed products. Through these and other traditional management techniques, I believe we will successfully address any dissenting opinions, and I am committed to evaluating our processes and refining them as necessary to ensure that there is a healthy and open scientific debate of issues at FDA.

Question 4. Surveys like the recent one of 997 FDA scientists conducted by the Union of Concerned Scientists and the Public Employees for Environmental Responsibility and the one conducted by the HHS Inspector General in 2002 paint a picture of FDA as an agency without the credibility of many of its own scientists, where science is being suppressed for reasons other than the interest of the public health.

Are you concerned that hundreds of senior level scientists at the FDA are reporting that they have been asked "for nonscientific reasons, to inappropriately exclude or alter technical information or their conclusions in a FDA scientific document?"

What will you do to ensure a culture of openness so that management both listens to and addresses scientific concerns about products regulated by the FDA?

Answer 4. I am committed to ensuring FDA makes decisions based on sound science. I will make myself personally available to staff who want to appeal decisions made by FDA management. I believe that the need to appeal to me will be rare, however, because I will ensure that there are strong policies and procedures in place for resolving issues involving dissenting opinions. Efforts toward that end will include promulgating new policies and procedures as necessary, and strengthening, by process improvement and best practices measures, many of those that are already in place.

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FDA AUTHORITY

Question 5. 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?

Answer 5. FDA is in the process of undertaking a review of the decisionmaking process behind requests for Post-marketing Study Commitments (PMCs) for human drugs, including biological drugs. An outside contractor has been hired to evaluate how different review divisions decide to request PMCs, decisions surrounding what kinds of PMCs to request, and what are reasonable timeframes for completing PMCs. The study will serve to assist FDA in harmonizing procedures. While this study is being conducted, the Centers within FDA have undertaken activities to improve the response on post-marketing and post-approval studies for human drugs (including biological drugs) as well as for devices. We do not believe that we need additional authority in this area.

Human drugs (including biological drugs).—Post-marketing study commitments (PMCs) for approved drug products are studies that a sponsor either is required or agrees to conduct after FDA has approved a product for marketing to further define the safety, efficacy, or optimal use of a product. In some cases, the studies can take years to complete, even if everything is going according to schedule. In other cases, there are considerable obstacles (e.g., difficulty in recruiting patients and investigators to participate in a clinical trial when an approved therapy is available) that must be addressed before the studies can be completed. In these cases, FDA works closely with sponsors to address these obstacles. It should also be noted that approximately 38 percent of the currently pending PMCs for new drug applications were established in applications approved between October 1, 2003, and September 30, 2005, and thus, depending on the complexity of the study, FDA would expect that many of these studies are in the development phase.

FDA takes its statutory obligations under the Food and Drug Administration Modernization Act of 1997 (FDAMA) to track and monitor the progress of PMCs

very seriously. FDA recently published a final guidance to industry to describe in greater detail the content, format, and timing of PMC annual status reports submitted by the drug industry. Furthermore, FDA reports annually in the Federal Register on the performance of applicants in conducting their PMCs and maintains a public Web site that contains the information that FDA is required under FDAMA to make available to the public. These initiatives, along with other FDA internal procedures, are all intended to ensure that industry undertakes their commitments and completes them in a timely manner.

Devices.—On January 1, 2005, CDRH initiated the use of the new Condition of Approval Tracking System. As of that date, all post-approval studies of class III devices are entered into the system, along with the due dates of any agreed upon report deliverables. The system is monitored daily to see that sponsors are honoring their commitments. Procedures are in place to notify the sponsor immediately if deadlines are not met, and also to acknowledge the receipt of reports that are on time and are reviewed. To date, under the new system, all reports have been delivered on time.

CDRH is also developing the Post-approval Study Web site that will be available to the public. This Website will list the post-approval studies being done, briefly describe the study, and document the status of studies, as reported by industry.

FDA believes that changes to the Condition of Approval study program will improve communication with industry about these studies and increase collaboration in designing high quality studies with targeted end points. The results of these studies will be important to FDA, industry and the health care community. Acknowledgement of receipt of study reports and followup on overdue reports will encourage compliance. Finally, we believe the public Website will prompt industry to do the studies and report to FDA on time.

In addition to the efforts regarding device Condition of Approval studies noted above, FDA continues to use its authority under section 522 of the act to order post-market surveillance studies of class II and class III devices meeting the statutory requirements of that section, to require the collection of useful data that can show unforeseen adverse events or other information necessary to protect the public health. Should a company subject to such an order fail to meet the requirements of the act and implementing regulations, FDA has authority to take enforcement action.

Question 6. 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. von Eschenbach, 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 6. I do not believe new statutory authority is needed. We use all existing regulatory authority and enforcement powers when negotiating label changes with drug companies or when monitoring or managing drug safety issues. FDA can and does successfully carry out its mission under its current statutory and regulatory authority.

Question 7. There is substantial public concern about the lack of resources committed to the Office of Drug Safety (ODS), as well as its relative lack of authority. Some have suggested that the ODS serves merely as a consultative body to the Office of New Drugs. Dr. von Eschenbach, during your testimony you said that you didn't see a need to change the current structure of the FDA.

However, given the events of the past couple of years including the withdrawal of Vioxx and controversy surrounding Ketek, do you believe the role and the authority of the ODS should change?

How will you ensure that the FDA staff responsible for monitoring the safety of drugs once they are on the market will have independence within the Agency and the resources necessary to protect the public's health?

Answer 7. We continue to believe that our current organizational structure, which keeps the debate about the safety and efficacy of a product in one FDA Center, is appropriate and effective. In the past year, we have moved to strengthen that structure by ensuring that the epidemiologists and post-market safety experts have equal organizational representation and stature within FDA's Center for Drug Evaluation and Research (CDER). With the reorganization, we established an Office of Surveillance and Epidemiology (OSE) that is responsible for most of the functions formerly managed by the Office of Drug Safety. This new name more appropriately rep-

resents the functions handled by the office and alleviates some of the confusion and misconception that drug safety issues are handled solely by one office in CDER. Further, the Director of OSE now reports directly to the Center Director, thus putting the OSE Director on the same footing with the OND Director when negotiating business and management issues including requests for resources. We believe that this structure fosters a proper environment for a fair assessment of the effectiveness and risk of a product.

Question 8. The administration's fiscal year 2007 budget includes an additional $5 million for drug safety.

With this budget increase, how many scientists will the ODS employ? How does the ODS budget and staff compare to that of the Office of New Drugs? Given that the ODS is charged with tracking every single drug that is on the market, does the balance of resources seem appropriate?

Answer 8. FDA requested $3.9M in additional funds in fiscal year 2007 to continue to modernize its Adverse Event Reporting System (AERS) and create "AERS II"—a replacement web-accessible computer system that will enable FDA to maintain the current level of AERS functionality, while providing enhancements in several areas.

These enhancements include adding capabilities planned in the original AERS. With over 5 years of experience with the database, we have identified areas of critical new functionality, including generating web-accessible adverse event information. The current AERS system is FDA's principal post-marketing monitoring tool. It allows FDA to identify events that were not observed or recognized before approval. It allows FDA to identify adverse events that might be happening because patients and prescribers are not using the drug as anticipated.

The AERS system alone is not adequate for a successful, state-of-the-art drug safety program. To appropriately monitor drug safety after marketing, it is essential that FDA have access to a wide range of clinical, pharmacy, and administrative databases, including databases maintained by organizations such as those maintained by the Center for Medicare and Medicaid Services, the Department of Veterans Affairs, the Department of Defense, and the Indian Health Service. We also access databases maintained by clinical and hospital networks and insurers, such as health maintenance organizations, preferred provider organizations, and insurers, and pharmacy benefit management organizations.

FDA is actively evaluating the utility and feasibility of conducting specific studies of high priority safety issues using such linked databases. Studies conducted on these types of databases will provide more evidence about drug use in a broader range of conditions, including more detailed evidence about drug safety in subgroups of patients.

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Earlier this year, the Center for Drug Evaluation and Research reorganized and established the Office of Surveillance and Epidemiology (OSE) that reports directly to the Center Director. This new office is responsible for most functions previously conducted by the "Office of Drug Safety," and the new name more appropriately represents the functions handled by the office and alleviates some of the confusion and misconception that drug safety issues are handled solely by one office in CDER. Currently, the fiscal year 2006 estimated budget for OSE is $34.5M, while the fiscal year 2006 estimated budget for OND is $110.9M. FDA ensures that adequate resources are devoted to the functions managed by both OND and OSE.

Question 9. 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) which Senator DeWine and I authored and the Pediatric Research Equity Act (PREA)—have led to enormous improvements in our knowledge about the appropriate use of drugs for children.

Dr. von Eschenbach, pediatric testing in children is particularly relevant in light of the recent questions about drug safety, and especially the possible adverse effects of antidepressants (SSRIs) when used to treat youth. Several SSRIs had been studied in children, but the results of those studies were inconclusive.

If confirmed as Commissioner, would you continue to support efforts to expand pediatric testing? 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? Is there additional authority that Congress can provide that would be helpful to the FDA?

Answer 9. I support efforts to expand testing drugs for use in pediatric patients. Both PREA and BPCA have been important tools for FDA in obtaining needed pediatric information. The legislative authority granted to FDA to obtain efficacy and safety data on products used in pediatric patients has allowed the Agency to re-label over 100 products with new pediatric use information and to disseminate this extremely valuable product information to the public. Among other examples, the SSRI studies in children that enabled FDA to identify concerns regarding suicidality associated with pediatric use of SSRIs, were conducted under the pediatric exclusivity incentive.

We are considering additional steps the Agency could potentially take to improve pediatric testing and to ensure that pediatric studies are answering the right questions and providing useful results. BPCA and PREA have created an environment which promotes the study of therapies in children. Considering that over 100 products have had new pediatric labeling and more than 25 percent of these products had new information on dosing changes or pediatric safety information, in addition to those that were now approved for a younger population, we think the program is already demonstrating the utility of studying products that are being used in the pediatric population.

Question 10. I have heard the concern that it is unclear whether the FDA has the authority to require labeling to clearly indicate when a product has been studied in children under BPCA or PREA and found to not be effective.

In other words, does the FDA have the ability to require a manufacturer to clearly differentiate on a label when a product is not approved for use in children because it has been shown through studies to be ineffective or unsafe versus when it is not approved for children because it has just not been studied in that population?

Answer 10. Increasingly, product labeling is being used to convey the current state of knowledge about the safety and efficacy of a drug in the pediatric population. We already have begun to implement an effort to ensure that label changes are made for all drugs for which studies are submitted under BPCA. These labeling changes aim to ensure that products studied under BPCA have labeling that includes more information than the statement "safety and efficacy had not been established in the pediatric population." Thus, where a study is inconclusive about safety or effectiveness, the labeling may describe the results of the study without stating that the drug should or should not be used in certain pediatric populations. Similarly, if FDA has information that establishes that a drug does not work in pediatric populations or if clinical trials reveal a safety concern, FDA would place that information in the labeling, even if the drug is not approved for use in the pediatric population.

Section 5 of the BPCA provides a process for timely labeling changes for drugs granted exclusivity, including a provision for referral to the Pediatric Advisory Committee. Although this process does not apply to labeling changes for studies performed under BPCA where exclusivity was not granted, nor for studies conducted outside of the scope of BPCA, we have moved forward to ensure sufficient information will be included in the label. The changes made in BPCA have been of great assistance in ensuring more prompt agreements once the supplement has been reviewed and acted on by FDA.

There is also legislative authority granted by PREA that allows us to require sponsors to include information in their label indicating that pediatric studies were waived because they believe the drug would not be effective in pediatric patients or because there are safety concerns for pediatric patients.

In spite of these improvements, FDA acknowledges that we use various terminologies in labeling to describe the results of studies and that some of the terminology used may not have clearly conveyed if data were collected in pediatric patients. FDA is working to improve the clarity of pediatric information included in labeling and will continue to do so.

Question 11. Currently, a number of safety protections are applied to products studied under BPCA, but not to products studied under PREA. For example, adverse events related to products studied under BPCA in the first year after exclusivity is awarded are reported to and reviewed by the FDA's Pediatric Advisory Committee. No such protection applies to products studied under PREA. Similarly, the results of all studies conducted under BPCA must be made public. No such requirement applies to products studied under PREA.

Do you think the legislation should be modified so that these requirements apply to PREA? Are there other ways in which PREA and BPCA could be better coordinated?

Answer 11. I appreciate your question and believe that both PREA and BPCA have been important tools in obtaining needed pediatric information to treat pediatric patients. We have been reviewing possible improvements that could make the program even more effective. Our review is not yet complete. If we determine new legislative proposals are necessary, we will look forward to working with you to enhance the program.

PEDIATRIC MEDICAL DEVICES

Question 12. I was pleased to hear you testify that, if confirmed, you would enhance opportunities for pediatric medical devices. This is an issue of great importance to me. 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.

If confirmed, what steps would you take to enhance opportunities for new device development for children?

Answer 12. Although cutting-edge research and revolutionary technologies have led to the development of new innovative devices, pediatric device development faces additional challenges that may cause it to lag behind adult device development. The type of applicants (small companies) and obstacles to the development of pediatric devices, including the difficulties in conducting device clinical trials involving children, make this issue extremely challenging. FDA believes that communication between the Agency, industry, patients, and clinicians is essential for fostering pediatric device innovation. To this end, CDRH has been focusing on increasing interactions among these parties during product development and pre-market review.

CDRH is working to develop more device-specific guidances that would, when appropriate, include advice for manufacturers on issues such as the type of modifications, testing, and/or labeling changes needed for the device to be used in pediatric populations. CDRH is also holding workshops to discuss the development of critical pediatric devices, which include a 2005 advisory panel meeting to discuss clinical trial designs for, and ethical issues related to, the evaluation of devices to treat pediatric obesity; a 2006, FDA sponsored a workshop for manufacturers of pediatric left ventricular assist devices intended for infants and children from 2 kg to 25 kg with congenital or acquired cardiovascular disease, and a public workshop held in collaboration with NIH to identify new approaches to evaluating fetal intrapartum monitoring devices, including the possible development of a large validated test database.

Question 13. What is the FDA doing to ensure that devices used in children are designed and sized for their use? Can the FDA currently track how many devices have been approved for children and the number produced for conditions that occur in children? Would the FDA find a mechanism for tracking pediatric device approvals useful?

Answer 13. There are many challenges to the design and development of pediatric devices. Long-term or permanent implants need to "grow" with the child or at least remain functional as the child develops. The devices also need to have a longer life span. In general, children require smaller devices, often requiring re-engineering of the entire product to ensure its functionality remains consistent as the child grows.

Increased communication between the Agency, industry, patients, and clinicians is essential for encouraging pediatric device innovation and ensuring that the devices are appropriately designed. Therefore, CDRH has been focusing on these interactions during product development and pre-market review. Examples include:

The Center is working to develop more device-specific guidances to provide regulatory clarity for industry and encourages manufacturers to meet with review staff during device development to ensure that key questions specific to their device can be addressed and has issued a guidance regarding the type of data needed to support marketing of pediatric devices and the protection measures to be addressed when involving this population in clinical trials; CDRH has formed a pediatric steering committee (SC) to oversee pediatric issues throughout the Center. Its functions include facilitating and encouraging pediatric pre-market reviews and consults by

experts throughout the Agency, CDRH is holding workshops to discuss the development of critical pediatric devices.

Regarding tracking, FDA does not have a data system capable of tracking all studies, submissions, or approvals for pediatric devices, but as discussed below, we have made important strides in this area. Some medical devices are specifically designed for use on infants and children, such as infant incubators and infant radiant warmers, and each has a unique classification regulation associated with it. For these devices, we are able to identify the number of applications that have been cleared or approved. Under a provision in the Medical Device User Fee and Modernization Act of 2002, device submissions solely for pediatric use are exempt from user fees in order to encourage their development. FDA's user fee database allows us to identify those applications that seek to take advantage of this incentive. Most medical devices, however, are indicated for general use, which often includes pediatric use with the only difference being the size of the device available. Since these devices can be used in both the pediatric and adult populations, these are not specifically tracked as pediatric devices.

CDRH believes there are potential advantages in being able to track pediatric device submissions and approvals, and we are modifying our tracking systems to accomplish this. CDRH is currently making database changes, so that we will be able to track the number of PMAs, HDEs, and IDEs for pediatric indications in the near future.

In addition, FDA believes there may be value in tracking pediatric subpopulations (neonates, infants, children, adolescents) for both marketing and investigational applications. We are examining whether and how our current database can accommodate such tracking, as well as determining the resources necessary to making such changes.

Question 14a. Given some of the barriers that hinder new device development for children, how does the FDA think incentives could be improved to meet the pediatric need?

Answer 14a. FDA agrees that, although there are many devices that have been developed particularly for the pediatric population, there still remain a number of obstacles to studying and developing devices appropriately for use in children. The Agency has been working with several pediatric professional organizations to better understand this important issue. Representatives from academia, medical specialty organizations, the device industry, and several government agencies participated in a series of Pediatric Device Stakeholders meetings in the fall of 2004. It became evident during discussions at these meetings that finding effective solutions to improving the availability of pediatric devices raises complex issues. CDRH has issued a general guidance, "Pre-market Assessment of Pediatric Medical Devices—Guidance for Industry and FDA Staff" regarding the type of data needed to support marketing of pediatric devices and the protection measures that should be addressed when this patient population is involved in clinical trials of such products. The Center has also been working to develop more device-specific guidances to provide regulatory clarity for industry as they work on these new devices. FDA is also encouraging manufacturers to meet with the Agency during the development phase as questions and issues arise specific to these devices and/or the pediatric clinical data that may be needed to support their marketing.

Question 14b. Would establishing a nonprofit consortium to promote pediatric device development be useful?

Answer 14b. The idea of a pediatric device consortium was raised and discussed at the Pediatric Device Stakeholders meetings held in the fall of 2004. Depending on how it is constructed, it may be an effective way to promote pediatric device development. During the Stakeholder meetings, it was also recommended that a mechanism be established to allow for information to be provided to the NIH pediatric device contact regarding those specific pediatric device needs that the Consortium lacks sufficient funds to support and those needs for which the Consortium has been unable to stimulate manufacturer interest. It was also recommended that the Consortium coordinate with FDA and the device companies to ensure that adequate safety and effectiveness data, as defined by FDA, is developed for these new technologies.

Question 14c. Would granting the FDA Pediatric Advisory Committee explicit authority to monitor pediatric devices and make recommendations for improving their availability and safety be helpful in increasing children's access to medical devices that are safe and effective?

Answer 14c. In response to whether granting the FDA Pediatric Advisory Committee (PAC) explicit authority to monitor pediatric devices and make recommenda-

tions for improving their availability and safety would be helpful in increasing children's access to safe and effective medical devices, CDRH believes that the panel members available under its own Medical Devices Advisory Committee, as well as the expertise of available members on other committees, including the FDA PAC, provide the pediatric experience needed to adequately monitor the safety of pediatric devices and facilitate their development.

Question 15. In order to improve post-market surveillance of children's medical devices, would you agree with the recommendations made by the Institute of Medicine (IOM) in a July 2005 report on the adequacy of post-market surveillance of pediatric medical devices that strongly suggests establishing a publicly accessible database of post-market studies and increasing FDA authority to require post-market studies?

Answer 15. FDA agrees with the IOM recommendation to establish a publicly accessible database of post-market studies. To that end, FDA has been working on the following:

• FDA issued a draft guidance entitled, "Procedures for Handling Post-approval Studies Imposed by PMA Order" to enhance the efficiency and effectiveness of conveying information on post-approval studies (PAS) to the Agency and for the Agency's review of such information. This guidance will assist industry in the pre-approval stage as they proceed to develop PAS.

• In its draft guidance, FDA also proposed that periodic public presentations to FDA's Medical Device Advisory Panels on the status of these studies be made by the industry and FDA. FDA believes that this will lead to a better informed public and clinical community and will provide important feedback to the Panels that often recommend that these studies be conducted.

• An electronic tracking system was developed and implemented to monitor the status of all PAS.

• A web page listing the status of PAS is under development and expected to be available late in 2006.

FEDERAL PREEMPTION OF STATE DRUG LABELING

Question 16. On February 23, 2006, Senator Kennedy and I wrote Secretary Leavitt with our concerns about the final rule published on January 18, 2006 in the Federal Register amending 21 CFR parts 201, 314, and 601. The rule modifies drug labeling requirements in order to give information to physicians in a more concise and appropriate manner. On March 15, 2006, I received a letter from LaJuana D. Caldwell, Director, FDA Executive Secretariat informing me that a thorough response to my letter was being prepared at FDA. To date, my office has received no response from the FDA and several attempts to obtain information about when the response would be sent have gone unanswered. I am deeply concerned about the preamble to the final rule which asserts broad and vague Federal preemption of State drug labeling, advertising, and product liability laws. As I stated in my letter, such an assertion is inconsistent with long-standing FDA practice and congressional intent, not to mention the fact that such a drastic reversal of policy should be subject to public consideration and public comment on whether the Agency has the legal authority to preempt State requirements. When will we receive a response from the FDA to our letter?

Answer 16. My apologies for the delay—we are working to provide a substantive response to your letter as soon as possible.

Question 17. In the December 2000 proposed rule, the Agency stated that the regulations would not preempt State law. However, the preamble of the final rule asserts that it has been the Government's "longstanding" position that State actions related to drug labeling and advertising, and even medical malpractice, are preempted. Can you please provide examples of this "longstanding" position and provide all Agency statements before 2001 with respect to this issue?

Under the Federal Food, Drug and Cosmetic Act, the FDA is charged with ensuring that drugs and devices are safe and effective and that the labeling of drugs and devices adequately informs users of the risks and benefits of the product. FDA scientists work continuously to evaluate information submitted by the sponsor and the latest available scientific information to monitor the safety of products and to incorporate information in the product's labeling when appropriate. The FDA considers itself to be the final arbitor of the content of drug and device labeling, and believes this is further substantiated by the courts in response to briefs filed by the Agency in support of preemption dating back to at least 1977.

Answer 17. In the preamble to the final rule, FDA was stating the Agency's position on the State of the law as it relates to Federal preemption and drug labeling.

The act has long given FDA the authority to determine when drug products are misbranded. FDA therefore, is the appropriate arbiter regarding what drug labeling is considered false and misleading. FDA was simply restating its views about this congressionally assigned role with regard to State failure to warn claims based on FDA approved labeling. This has long been FDA's position and DOJ has participated on behalf of FDA in preemption cases. Additionally, FDA has advanced this position in rulemakings, prior to this administration. Indeed, FDA filed briefs during the previous administration taking the position that the Supremacy Clause bars State tort liability for failure to include a warning on a drug label that is in conflict with or contrary to the warnings approved by the FDA. See, e.g., *Bernhardt* v. *Pfizer, Inc.*, No. 00 Civ. 4042 (LMM), Statement of Interest of United States (S.D.N.Y. filed Nov. 13, 2000). Furthermore, FDA rules dating back to at least 1979 reflect the Agency's views that the ultimate decision whether to require a warning on a drug label rests with FDA, and that Federal law prohibits inclusion of statements on a label that FDA has determined not to be supported by substantial evidence. See, e.g., 44 Fed. Reg. 37434, 37435, 37441, 37447 (1979).

FDA's regulation of prescription drug labeling, and Federal preemption over conflicting State requirements, is extremely important to FDA's ability to protect the public health. FDA's regulation of prescription drugs is designed to ensure each drug's optimal use through requiring scientifically substantiated warnings. Under the Federal Food, Drug, and Cosmetic Act, FDA is the public health agency charged with ensuring that drugs and devices are safe and effective, and that the labeling of drugs and devices adequately inform users of the risks and benefits of the product. FDA employs scientists and other experts who review the information submitted by the manufacturer on a product's risks and carefully titrate the warnings, etc. that should be placed on the labeling. FDA continuously works to evaluate the latest available scientific information to monitor the safety of products and to incorporate information into the product's labeling when appropriate. The public health risks associated with overwarning are as great as—if not greater than—the health risks associated with underwarning. Overwarning can cause patients not to take beneficial drugs and doctors not to prescribe them. Under-utilization of a drug based on dissemination of scientifically unsubstantiated warnings, so as to deprive patients of beneficial, possibly lifesaving treatment, could well frustrate the purposes of Federal regulation as much as over-utilization resulting from a failure to disclose a drug's scientifically demonstrable adverse effects. Further, allowing unsubstantiated warnings may also diminish the impact of valid warnings by creating an unnecessary distraction and making even valid warnings less credible.

Question 18. Under Executive Order 13132, issued by President Reagan and reissued by President Clinton, a Federal Agency such as FDA must consult with State and local authorities about, and examine, the effects on States and localities of each regulation it issues. In the proposed rule, FDA indicated that the regulation would not preempt State law and, as such, States did not comment on it. Can you please describe what the FDA did to consult with State and local governments about this regulation?

Answer 18. In adopting the final rule in 2006, FDA did consult with a number of organizations representing the interests of State and local governments about the potential interaction between FDA drug labeling requirements and State law. *See* 71 Fed. Reg. 3922, 3969 (2006). FDA contacted several representative State groups, explained that FDA was considering including language explaining its position on preemption in the preamble to the final Physician Labeling Rule, and considered all responses it received. Furthermore, it is worth noting that the U.S. Supreme Court has suggested that Federal preemption would apply even if the Agency explicitly stated at the time it promulgated regulations that the regulations were not intended to have preemptive effect, if the Agency subsequently changed its view on the strength of its interests in preemption or the effect of the regulations in question. *Hillsborough County* v. *Automated Medical Laboratories, Inc.*, 471 U.S. 707 (1985).

DIRECT TO CONSUMER (DTC) ADVERTISING

Question 19. 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. 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 19. The Federal Food, Drug, and Cosmetic Act (FDCA) and Agency regulations focus on the content of prescription drug promotion. The law does not prohibit advertising prescription drugs directly to consumers, and the First Amendment

does not permit the banning of truthful, nonmisleading commercial speech. Monitoring DTC promotion, and especially broadcast ads, is a top priority. FDA works to ensure that information about product claims and risks is presented in a way consumers can understand. We also want to ensure that consumers get balanced, truthful, and nonmisleading information consistent with the First Amendment, and are committed to do this.

FINAL UVA/UVB MONOGRAPH FOR SUNSCREEN

Question 20. The Fiscal Year 2006 Agriculture Appropriations Conference Report included language directing the FDA to complete the final sunscreen monograph, which will guide UVA and UVB labeling information for over-the-counter (OTC) sunscreen products, within 6 months of passage of the agriculture appropriations bill. That bill was signed into law on November 10, 2005 and the deadline for the final monograph was May 10, 2006. It is now nearly 3 months past the deadline Congress set for the final sunscreen monograph—and the summer season is well underway—and yet the FDA cannot provide a date by which the final monograph will be released. The FDA began working on a monograph for sunscreen products in 1978 and has yet to complete it.

Dr. von Eschenbach, please provide the committee with the following information: An accurate time-line detailing a plan of action for completing the monograph; Any perceived or acknowledged obstacles to completing the monograph by the end of calendar year 2006; and a detailed explanation as to why the monograph has not been completed.

Answer 20. It is anticipated that a rulemaking will be issued by the end of calendar year 2006 to propose new testing and labeling, primarily for products that contain ingredients that block UVA rays. FDA drafted this proposed rule after asking for comments specific to this topic in a June 2000 *Federal Register* notice. As the Agency developed the rule, new issues emerged that needed to be addressed. For example, recently FDA received a citizen petition requesting that the Agency amend the OTC sunscreen drug monograph to consider OTC sunscreen drug products containing nanoparticles as not covered under the monograph and instead treat them as new drugs. The proposed rule is currently in clearance.

The period for public posting of comments associated with the proposed rulemaking, once published, is 90 days and FDA will subsequently issue a Final Rule. The time to publication of the final rule is dependent on the number and content of the comments submitted in response to the proposed rule and the Agency's clearance process.

PSEUDOEPHEDRINE

Question 21. Pseudoephedrine (PSE) is a safe and effective decongestant in many over-the-counter (OTC) medicines for treatment of the common cold and hay fever. However, PSE also is a precursor chemical being diverted to illicit manufacturing of methamphetamine. Addressing this critical public health and safety problem necessitates transitioning consumers relying on PSE-containing OTC products to therapeutically-equivalent replacements that cannot be used in meth production.

During 2005, the Congress took action, reflected in the Conference Report on the Combat Meth Act, to facilitate FDA approval of such reformulated OTC products. Some longstanding OTC medicines that currently contain PSE and are marketed under the applicable FDA monograph potentially can be reformulated to include an alternate active ingredient in accordance with the steps Congress took in the Combat Meth Act.

As we approach the September 30th effective date of the Combat Meth Act, Congress understands there is a similar opportunity to facilitate development of new prescription products that could be approved by FDA as safe and effective therapeutic alternatives to fill the need currently met by PSE that could provide similar therapeutic benefits and be equally convenient, but without the diversion or abuse risks associated with PSE.

Can you please update the committee on efforts the FDA is taking, in advance of the September 30th effective date of the Combat Meth Act, to implement that statute and its provisions addressing pseudoephedrine-based meth diversion?

Answer 21. While the primary responsibility for implementation of the Combat Meth Act is with the Department of Justice (DOJ), FDA has acted to ensure regulated industry understands its obligations with respect to FDA-regulated products. Immediately after enactment, we provided manufacturer and drug information to the Drug Enforcement Administration (DEA) needed for DEA's rulemaking on manufacturer production and import quotas, part of the Combat Meth Act.

Also, the Office of Non-Prescription Products (ONP) is interacting with manufacturers to help them interpret the Combat Meth Act provisions for packaging of both NDA and OTC monograph products. For example, OTC products that are marketed under the OTC Drug Review may be reformulated following the stipulations for active ingredients, manufacturing, and labeling that are set out in the regulations associated with the OTC monographs. These reformulations do not require approval by the FDA prior to marketing. Accordingly, an immediate release tablet containing pseudoephedrine as a decongestant in combination with an antihistamine could be reformulated under the monograph to contain an alternative decongestant, phenylephrine, in combination with the same antihistamine. This reformulation would not require prior approval, supporting a rapid transition from products containing pseudoephedrine to products using other antihistamines. In addition, a new salt of phenylephrine was recently added to the monograph to allow manufacturers more flexibility in formulating products.

In addition, OTC products that are marketed under New Drug Applications (NDAs) require FDA review and approval prior to marketing of a reformulated product. Such supplementary applications are reviewed under the specific timelines and procedures associated with the Prescription Drug User Fee Act (PDUFA) and other pertinent regulations. ONP interacts with applicants to insure that only essential testing is required to demonstrate that the reformulations will be safe and effective. For instance, applicants would, in general, not be required to conduct clinical trials to demonstrate the safety and effectiveness of a product reformulated to include phenylephrine in place of pseudoephedrine. Applicants would instead be able to demonstrate the bioequivalence of the new product in humans compared to reference standards, a lesser demand on applicant resources.

Question 22. Through the appropriations process, Congress has directed the FDA Commissioner to encourage, expedite, and support the filing, review, and final action on any new drug application, or supplement to a new drug application, seeking approval of a combination of active ingredients previously-approved as safe and effective, that would replace or provide a therapeutic alternative to a currently-marketed drug product that contains an active ingredient that currently is the subject of diversion and/or abuse outside regulated channels of commerce.

In light of this directive, would you please delineate for the committee the steps that FDA has taken to enhance access to new prescription combinations of safe and effective marketed drugs that could provide alternative therapies to replace pseudoephedrine-containing products and address major public health and safety concerns arising from meth production?

Answer 22. Products which require New Drug Applications (NDA) or a supplement to an NDA (SNDA) may qualify for a priority review. We will meet with applicants to determine if such applications qualify to be considered under priority review. The ability to actually develop such a formulation and provide data to demonstrate that it is abuse resistant (and not simply defeatable by another mechanism) is complex. We interact with such applicants to ensure that only essential testing is required to demonstrate that the reformulations will be safe and effective. For instance, clinical trials are not required in any instance in which a demonstration of bioequivalence in humans can be appropriately applied. This may help shorten the time necessary to provide data for the NDA or SNDA. We also will respond to submissions and meeting requests quickly so that access is not delayed based upon the ability of a company to get feedback or to interact with the Agency.

QUININE SULFATE

Question 23. This past June, the FDA published a guidance document regarding drugs that are widely marketed without FDA approval which stated that the marketing of these drugs is unsafe and illegal because, "unapproved drugs have bypassed the Agency approval process through which FDA ensures, based on reliable scientific data, that marketed drugs are safe, effective, properly manufactured, and accurately labeled."

The FDA also stated,

> "FDA is dedicated and determined to meet our drug safety mission and to ensure that ALL drugs marketed in the United States meet safety, effectiveness, manufacturing, and labeling standards."

Quinine sulfate was one of the marketed drugs that had never been approved by FDA, but a year ago FDA granted approval to one company and required that its labeling include expanded safety information to address the serious risks of this drug. The company was also granted a 7-year Orphan Drug Exclusivity meaning it is the only company legally allowed to sell quinine during this period. However,

FDA has continued to allow the importation and marketing of numerous unapproved quinine products with outdated safety labeling.

Dr. von Eschenbach, in light of the serious safety risks of unapproved quinine products, when will FDA begin taking enforcement action against these illegal products?

What have been the barriers to FDA enforcement against domestic sales of unapproved quinine sulfate?

Answer 23. While the FDA drug approval system is widely recognized for bringing safe and effective new drugs to the market, it is unfortunate that many older or existing drug products continue to be marketed in this country without required FDA approval. The Marketed Unapproved Drugs Compliance Policy Guide (CPG) (*http://www.fda.gov/cder/guidance/6911fnl.pdf*) published in June addresses this issue and is a significant step forward for our drug safety initiative.

Because it is impossible for the Agency to simultaneously and immediately remove all unlawfully marketed, unapproved products from the market, the CPG outlines a prioritized, risk-based enforcement approach that encourages companies to independently comply with the drug approval process and ensure the safety and efficacy of their marketed products. The CPG discusses how the Agency will bring unapproved drugs into the approval process, while making every effort to avoid adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting patient access to drugs that may provide important health benefits. The Agency's enforcement resources are limited and need to be used strategically to maximize the protection of the public health.

With regard to quinine, FDA is aware of both the approved and unapproved quinine sulfate drug products on the market. FDA is evaluating the unapproved quinine drug products that are currently being marketed and will consider enforcement action consistent with the CPG.

RESPONSE TO QUESTIONS OF SENATOR HARKIN BY ANDREW C. VON ESCHENBACH

Question 1a. The FDA has made significant strides the past couple of years in implementing and enforcing DSHEA. 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 DSHEA gives the FDA sufficient authority to regulate dietary supplements?

Answer 1a. The Dietary Supplement Health and Education Act of 1994, or DSHEA, provides FDA the authority to act against dietary supplements that carry unsubstantiated claims or claim to treat diseases, that are unsafe, or that are otherwise adulterated or misbranded. We believe that the current statute provides the necessary authority and FDA is focused on effective implementation and oversight of dietary supplements.

On August 17, 2006, the U.S. Court of Appeals for the Tenth Circuit in Denver upheld the Food and Drug Administration's (FDA) final rule declaring all dietary supplements containing ephedrine alkaloids adulterated, and therefore illegal for marketing in the United States, reversing a decision by the U.S. District Court for the District of Utah. The Tenth Circuit Court of Appeals' ruling demonstrates the soundness of FDA's decision to ban dietary supplements containing ephedrine alkaloids, consistent with DSHEA.

On November 4, 2004, FDA published a Regulatory Strategy for the Further Implementation and Enforcement of DSHEA, in which FDA detailed specific steps for the further implementation of DSHEA. This Regulatory Strategy identified three specific initiatives: (1) monitoring and evaluating product and ingredient safety, (2) assuring product quality through CGMP regulations, and (3) monitoring and evaluating product labeling. With this strategy, FDA intends to improve the transparency, predictability, and consistency both of the Agency's scientific evaluations of dietary supplement product and ingredient safety, and of its regulatory actions to protect consumers against unsafe dietary supplements.

Question 1b. When we had Dr. Crawford's nomination hearing, he assured me that Good Manufacturing Practices for dietary supplements would be released "very soon." In addition, when you came before the Agriculture Appropriations sub-committee earlier this year, I asked you when they would be released. You replied that they were at OMB. DSHEA was passed in 1994. That means it's been 12 years and still we do not have GMPs for dietary supplements. Can you give us a definitive date as to when the final GMP regulations for dietary supplements will be published in the Federal Register?

Answer 1b. FDA is committed to publishing this final rule. I can assure you that there has been significant work done on the final rule since the comment period for the proposed rule ended in August 2003.

Since we are still in the rulemaking process, I can not tell you what specific issues are being discussed, but I can tell you that the issues have been complex, legally and substantively, and in some cases, novel. The final rule is under review by the Office of Management and Budget.

We have expended significant internal resources on reviewing and preparing responses to the comments received. We also have worked extremely hard to draft the final rule in order to assure quality products for the consumer while minimizing the economic impact to the dietary supplement industry. I can assure you that full attention is being given to the completion of the rule as soon as possible.

FDA RESOURCES

Question 2. Over the past several years, I have become increasingly concerned that FDA does not have the resources to adequately do its job. FDA regulates 25 cents of every dollar spent in the United States. Yet, in many areas, it seems FDA cannot keep up with its workload. For example, approval of generic drugs, and cuts at the Center for Food Safety and Applied Nutrition. You have new responsibilities with avian flu and threats to the food supply. At the same time, Congress is continuing to put new responsibilities on FDA. For example, last week we had a hearing in this committee on a National Food Uniformity bill that would increase the burden on FDA. And we will consider legislation next year that will give FDA more authority to do post-market surveillance of drugs.

You have been at FDA for almost a year now. In your candid opinion, does FDA have the resources to do its job effectively, efficiently, and quickly? If you look at the Agency, what specific areas do you think require more funding from Congress?

Answer 2. At FDA, our goal is to maximize the benefits of, and minimize the risks associated with the wide variety of products we regulate. The President's fiscal year 2007 budget proposes increases to respond to a number of high priority public health concerns. These increases reflect the areas of FDA responsibility that require increased funding from Congress. FDA has requested fiscal year 2007 increases for pandemic preparedness, food defense, critical path, drug safety, tissue safety, funding to meet user fee triggers, pay increases for cost of living, and increases to support our essential infrastructure needs. In the months since the President released the fiscal year 2007 budget, I have been working with the members of the House and Senate Appropriations Committees and others in Congress to secure these important funding increases.

FDA AUTHORITY OVER TOBACCO PRODUCTS

Question 3. As you know, tobacco use is the leading preventable cause of death in the United States, killing more than 400,000 people every year. Thirty percent of all cancer deaths are attributable to tobacco use. Nearly 4,000 children have their first cigarette everyday, and 1,500 of them become daily smokers. Senator DeWine has introduced legislation that would give the FDA the legal authority to regulate tobacco. The Senate has passed this legislation once and polls show overwhelming public support for this legislation. Do you support giving the FDA regulatory authority over tobacco products?

Answer 3. I share your concern that tobacco use is a vital public health issue. As you know, on March 21, 2000, the U.S. Supreme Court affirmed the decision of the U.S. Court of Appeals for the Fourth Circuit that the Food and Drug Administration (FDA) lacks jurisdiction under the Federal Food, Drug, and Cosmetic Act to regulate cigarettes and smokeless tobacco products.

RESPONSE TO QUESTIONS OF SENATOR MIKULSKI BY ANDREW C. VON ESCHENBACH

Question 1. GAO said in their recent report that the process for assuring the safety of drugs on the market is deeply flawed. They do not believe the Offices of Drug Safety, the Office of New Drugs, nor the Drug Safety Board are effectively addressing safety issues. Many, including Senators Grassley and Dodd with their legislation, have suggested an independent agency to provide the necessary oversight.

What do you think of the establishment of an independent watchdog body to ensure ongoing safety? How can the FDA be a watchdog of itself? Given the GAO report, please outline what changes you will make to assure the safety of drugs after they have been approved for the public?

Answer 1. Senator, we continue to believe that our current basic organizational structure which keeps the debate about the safety and efficacy of a product in one

Center is appropriate and effective. In the past year, however, we have moved to strengthen that structure by ensuring that epidemiologists and post-market safety experts have equal organizational representation and stature within the Center. Prior to the Center reorganization, the Director of the "Office of Drug Safety" reported to the Director of the Office of Pharmacoepidemiology and Statistical Science; whereas, the Director of the Office of New Drugs reported directly to the Center Director. With the reorganization, we established an Office of Surveillance and Epidemiology (OSE) that is responsible for most of the functions formerly managed by the Office of Drug Safety. This new name more appropriately represents the functions handled by the office and alleviates some of the confusion and misconception that drug safety issues are handled solely by one office in CDER. Further, the Director of OSE now reports directly to the Center Director, thus putting the OSE Director on the same footing with the OND Director when negotiating business and management issues including requests for resources. With this organizational change, we believe that our current structure fosters a proper environment for a fair assessment of the effectiveness and risk of a product.

You refer to the GAO Report on Drug Safety. Overall, FDA believes that the report is well done and that the conclusions reached are reasonable and consistent with actions we already have underway or planned. In particular, CDER has several initiatives that are discussed in the GAO report and are in the process of being implemented. These initiatives are aimed at strengthening the management of identified safety issues to assure that the decisions are made promptly, and are based on all of the relevant expertise in CDER, including the staff in OND and ODS.

While two separate and independent centers may be a logical organizational structure for distinct pre-approval and post-approval regulatory activities, the nature of our knowledge of a drug's safety profile and the expertise required for the ongoing assessment of a drug's risk-benefit balance demand that these two activities be housed in a single center. Our knowledge of a drug's safety profile proceeds along a continuum, which begins with *in vitro* and animal studies (before the drug is ever administered to humans), continues to grow through rigorous clinical trials, and is further refined after a drug is marketed. It is the review and synthesis of this cumulative knowledge base that leads to the most accurate assessment of the drug's safety profile. In CDER, Office of New Drug (OND) staff is the most knowledgeable about the pre-marketing safety data, while Office of Surveillance and Epidemiology (OSE) staff specializes in the post-marketing safety issues. Staff from the OSE and OND work closely in the analysis of appropriate regulatory actions, together they take into consideration both risk and benefit information from pre- and post-approval sources. If pre-approval and post-approval functions were split, there would be a loss of continuity in the review of risks and benefits.

Additionally, separating these two activities into two centers would be very costly, because of the duplication of the wide range of expertise involved. Medical officers in OND whose areas of expertise include the affected patient population(s), medical conditions, and treatments, know the results of animal and clinical studies that supported approval of the product; in addition, they review studies with products that are used in the same patient populations, and products, some still in the investigational phase, from drugs in the same or related classes. This expert knowledge of the patients' medical conditions, availability of alternative therapies, and safety profiles from IND and NDA submissions is a crucial component in the review of newly identified risks and how they may impact benefits. OSE personnel provide expertise in the areas of epidemiological studies of large populations, evaluation of data from AERS (that is, spontaneous adverse event reporting) and large external data sets purchased for adverse event tracking and evaluation in specific populations, medication error prevention, and risk management techniques.

If the responsibilities were split into two centers, the safety center would have to duplicate the expertise of OND staff, with expert knowledge of patient populations, medical conditions, alternative therapies, and safety profiles from investigational new drug applications and studies in marketing applications to support approval to enable the safety center to make appropriate risk-benefit decisions and the drug approval center would have to duplicate the expertise of the OSE staff. Cross-center consultation would be much more difficult, and therefore, less efficient, than within center collaboration.

OND routinely meets with OSE staff to discuss the current or anticipated safety of marketed products. In addition, CDER has recently instituted safety meetings that are held periodically (monthly or bi-monthly) to discuss new safety issues and the status of reviews and analysis of previously identified safety signals. Also, prior to approval of applications to market new molecular entities (NMEs), or nonNMEs, OND and OSE staff have pre-approval safety conferences. The OSE staff is also consulted by OND in many pre-approval activities that increase CDER's ability to un-

derstand and adequately monitor risk and benefit for marketed products such as medication error prevention and risk management plan review.

For the reasons mentioned previously—resources, communication, collaboration, leadership, and shared responsibilities—I do not believe that two separate and independent centers would improve FDA's ability to fulfill its mission to protect the public health.

Question 2. The FDA has always been the gold standard in maintaining drug safety, yet today, the Agency is being politicized and degraded. We have seen a persistent pattern of placing ideology before science.

As commissioner, outline for me what you will do to ensure that the best possible science informs the decisions the FDA makes every day? What are your concerns that hundreds of scientists at the Agency are reporting such interference with their scientific work? What would you as a scientist and Commissioner do to ensure greater respect for science within the FDA? Will you commit to having a channel for dissent if there are other views?

Answer 2. Senator, first and foremost, I am committed to ensuring FDA makes decisions based on sound science. I would like you to know that I will make myself personally available to staff who want to appeal decisions made by FDA management. I believe that the need to appeal to me will be rare, however, because I will ensure that there are strong policies and procedures in place for resolving issues involving dissenting opinions. Efforts toward that end will include promulgating new policies and procedures as necessary, and strengthening, by process improvement and best practices measures, many of those that are already in place.

For example, we are working to ensure a rigorous ombudsman program through which staff are welcome to promulgate dissenting opinions. Staff may also invoke standard written procedures for facilitating and resolving differing professional opinions. In addition, at the direction of the Secretary, FDA, established a Drug Safety Oversight Board whose charter includes responsibility for deliberating on any dissenting opinions raised during evaluation of drug applications and surveillance of marketed products. Through these and other traditional management techniques, I believe we will successfully address any dissenting opinions, and I am committed to evaluating our processes and refining them as necessary to ensure that there is an open scientific debate of issues at FDA.

Question 3. The scientists at the FDA are my constituents. In a recent survey done by the Union of Concerned Scientists, nearly half of them report their morale as "poor" or "extremely poor." Over half say their personal job satisfaction at FDA has decreased over the past few years. Only one-third think the Agency is moving in the right direction.

Dr. von Eschenbach—these are my constituents. As a scientist, what will you do to address their concerns? The FDA needs to re-establish its relationship with its own scientists. What will you do to ensure that the FDA will continue to recruit and retain the best and brightest employees?

Answer 3. FDA's workforce is comprised of over 12,000 incredibly talented and highly trained professionals who epitomize the true meaning of the word public servant. It is important for everyone to know that if confirmed, their support and guidance will be my greatest asset in leading the FDA.

As the FDA regulates almost 25 percent of all the products Americans consume, its talented and dedicated employees continue to set the Gold Standard that is emulated around the world but never equaled. This standard of achievement must not change. But the world around us is changing and the FDA of today is faced with new challenges and the FDA of tomorrow will encounter incredible opportunities.

Senator, I am committed to recruiting and retaining top staff to face these new challenges and to support the Agency's important public health mission.

Question 4. The FDA has always been the gold standard in maintaining drug safety, yet today, the Agency is being politicized and degraded. We have seen a persistent pattern of placing politics before science stifling scientists whose findings do not meet political objectives making decisions based on politics—rather than sound science. The FDA needs a major overall and a culture change at the highest levels in order to continue to meet its mission.

Dr. von Eschenbach, do I have your commitment that you will transform the FDA back into the proud agency it once was? What will you do, or have you done in your role as Acting Commissioner, to demonstrate a commitment to change?

Answer 4. I am committed to maintaining the long-standing traditions and values of an Agency whose processes and decisions are guided by sound science and vigorous analysis of evidence and based on the best interests of the patients and public we serve.

This year, FDA celebrates 100 years of successes in becoming the world's gold standard for assuring the drugs we give our children, the medical devices we use to treat disease and the food we eat is safe and effective. With more than 12,000 employees, FDA is committed to continuously improving and becoming even better as we enter our second century. FDA is as committed as ever to its time-honored tradition of encouraging vigorous debate among experts who use disciplined processes to arrive at consensus and conclusions.

Much work remains to fully equip FDA to face the challenges and seize the opportunities ahead, but I am confident that we are on the right path. I believe I can provide the leadership and management that will guide this important public health agency proudly and effectively into its second century of service.

RESPONSE TO QUESTION OF SENATOR JEFFORDS BY ANDREW C. VON ESCHENBACH

Question 1. You have had a very distinguished career and are a top scientist. What are your reasons for wanting the top FDA slot?

Answer 1. Throughout my career as a physician I have endeavored to devote my skills and effort to serving the needs of patients. In my career as a researcher, educator and administrator, I have witnessed remarkable achievements in science and technology that now hold the promise for extraordinary breakthroughs in conquering disease and assuring health for all. The FDA is the critical link between that phenomenal progress and its availability for the benefit of patients and the public. The FDA must assure that safe and effective life saving and health enhancing interventions are made available in the shortest possible time. The next few years are crucial to creating the FDA of the 21st century—an FDA that uses the tools of modern molecular science to facilitate the regulation of the food, drugs, devices and products that society will require to lead long and healthy lives. The Agency must swiftly adopt modern management tools to enhance the efficiency and reliability of the regulatory process to continue to fulfill its covenant to protect and promote public health. It would be my lifelong professional dream come true for me to be confirmed by the U.S. Senate, and to have the privilege to serve as the Commissioner of the FDA as it embraces these opportunities and challenges.

RESPONSE TO QUESTIONS OF SENATOR BINGAMAN BY ANDREW C. VON ESCHENBACH

LEAD IN IMPORTED CANDY

Question 1. For some time, those of us concerned about the health and well-being of Hispanic children (both in the United States and in Mexico) have eagerly awaited action by the Food and Drug Administration (FDA) to reduce the acceptable level of lead in candy to ensure that children's exposure to lead is minimized, as the Agency committed to do in Spring 2004. We have been concerned particularly about imported candy from Mexico. Therefore, in a letter I wrote you in January, I explained that I was pleased to see that, through its December 2005 draft guidance, the FDA has proposed that acceptable levels of lead in candy be reduced from no more than 0.5 part per million (ppm) to 0.1 ppm, while also maintaining the enforcement policy toward the use by industry of lead-based printing ink on candy wrappers. I expressed my strong support for both of these actions.

However, I have been deeply disturbed by the fact that, while FDA states it will maintain its enforcement policy against industry use of lead-based printing ink on candy wrappers, it appears to be gutting its enforcement policy with respect to the acceptable level of lead in the candy itself. Dropping the stated acceptable level from no more than 0.5 ppm to 0.1 ppm is meaningless if FDA does not intend to enforce the lower standard. The public documents on enforcement of the new 0.1 ppm standard appear to indicate just that—FDA is abrogating its current enforcement policy without replacing it with anything other than a "recommendation" with no teeth.

The notice published in the *Federal Register* on December 27, 2005, reads, ". . . FDA is rescinding previous guidance provided in a 1995 letter to the industry regarding an enforcement level." That would not be disturbing, in and of itself, if the guidance being rescinded were being replaced with new enforcement policy. However, the draft guidance and supporting documents make clear that is not the case.

As the draft guidance entitled, "Lead in Candy Likely To Be Consumed Frequently by Small Children: Recommended Maximum Level and Enforcement Policy" reads,

> "The 0.1 ppm recommended maximum lead level is not an enforcement guideline. FDA intends to consider several factors in bringing enforcement actions regarding lead in candy . . ., including the level of lead present and the best available consumption data."

The 0.1 ppm level is further undermined by the draft guidance's clarification that "FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required."

In addition, the supporting document for the guidance takes it one step further by stating, "The draft guidance also rescinds the 0.5 ppm guideline for considering enforcement action and does not announce a new enforcement guideline."

Further to the point, the *Baltimore Sun* (December 23, 2005) quotes Michael Kashtock, "a senior adviser at the FDA," as stating:

> "The guidance doesn't include enforcement because it's too difficult to have a 'one-size-fits-all approach' to various candies" and that 'the agency has met with Mexican officials and is hoping to prevent tainted candy from coming across the border.' FDA enforcement policy should not be based on 'hope.'"

In sharp contrast, the 1995 enforcement guidance read:

> . . . we have the authority to take regulatory action against any food product that contains a poisonous or deleterious substance that may render the product injurious to individuals. We also have regulations that require that ingredients used to manufacture food be safe, which requires that they be of a suitable degree of parity for their intended use. Further, our regulations require that equipment and utensils used in the production of food be designed and used in a manner that precludes contamination of the food with unsafe substances.

The statute clearly anticipates that FDA will set acceptable levels of contaminates, such as lead, in food products, and that, once such levels are established and exceeded, the product is adulterated and subject to enforcement action.

FDA's press release on the guidance stated that the Agency will

> "[c]ontinue to closely monitor the lead levels in Mexican candy and other domestic and imported candy products, work with our Mexican counterpart regulatory agencies, and take appropriate regulatory action. . . ."

Since FDA has apparently now rescinded the 1995 enforcement guidance, I asked that you take immediate action to clarify what the Agency means by "appropriate regulatory action." Further, I asked that you explain both how FDA will take action against manufacturers, importers, and distributors of candy that exceeds 0.1 ppm of lead, whether domestic or imported, and how the Agency will identify the most likely sources of violations and set enforcement priorities. This clarification is essential so we can be assured that you intend to protect our Nation's children, particularly Hispanic children and children along the U.S.-Mexico border, from dangerous lead exposure.

Furthermore, as part of that effort, I urged that FDA work in close partnership with the U.S.-Mexico Border Health Commission (USMBHC) to protect the health of children in both the United States and Mexico. FDA participated in a meeting in El Paso, Texas, on January 26–27, 2006. However, it is unclear whether any additional action has taken place in the last 6 months.

We know that elevated BLLs can have, as the California Senate Committee on Health and Human Services has found, "dramatic and devastating effects, particularly on children." The committee adds,

> "It affects the liver, kidneys, lungs, spleen, muscles, heart, and central nervous system. At high levels, lead poisoning can cause kidney problems, seizures, coma, miscarriages in pregnant women and low sperm counts in men, and even death. Once eaten, it stays in the bloodstream and bones. Even low levels of lead are harmful and are associated with decreased intelligence, impaired behavioral development, stunted growth, and impaired hearing."

Therefore, I once again urge your immediate attention to this important matter. It is crucial for our children that you immediately make public real enforcement policies and ensure appropriate regulatory action in cases where there is failure to comply with the new 0.1 ppm standard. Anything less will fail many of our Nation's children and force individual States to take action, as California and Illinois already have done, to protect their children.

With respect to California, while FDA has failed to take action, a lawsuit in California resulted in a settlement in June by California Attorney General Bill Lockyer in which three candy manufacturers agreed to substantially reduce the amount of lead found in imported Mexican candies that are popular with children.

As the Associated Press reported,

> "The attorney general's office led a coalition of government agencies and nonprofit groups who sued candy makers under a State law that requires warning

labels on anything that could cause cancer, birth defects or other reproductive harm."

What actions will the FDA take to ensure that all children are protected from lead in candy?

Furthermore, wouldn't the Food Uniformity Act that is currently moving its way through Congress have preempted the very action that the State of California used to protect the health and well-being of its children from lead in imported candy?

Answer 1. FDA is giving a high priority to its monitoring and enforcement activities aimed at imported and domestic candy products with potentially harmful levels of lead. FDA will take enforcement action whenever it encounters a candy product that contains potentially hazardous lead levels. Current findings of violative products are infrequent and have significantly decreased compared to the period prior to 2005–2006.

We have had meetings with industry representatives of Mexican candy companies. Mexican candy manufacturers are well aware of the importance of reducing lead levels in their products, and in anticipation of FDA's pending lower recommended maximum lead level, are likely to obtain washed chili for use in their products (unwashed chili was the major cause of elevated lead levels in candy containing chili).

FDA is continuing to work with the United States-Mexico Border Health Commission (USMBHC) on the issue of lead in candy, and also on other lead containing products such as pottery and folk remedies. USMBHC plans to hold a Bi-national Lead Meeting on September 28 and 29 in San Diego to:

1. Share information on the public health impact of exposure to lead in Mexican ceramics, cookware, candy and home remedies in the United States and Mexico,
2. Identify problematic issues for the United States and Mexico-related to these sources of lead, and
3. Identify collaborative binational initiatives to:
   a. Identify specific products posing health risks in the United States and Mexico because they are sources of lead exposure; and
   b. Identify nonlead based alternatives, and promote their manufacture and export to the United States.

FDA contributed to the data summary report on lead in candy that the United States will exchange with our Mexican colleagues from the Federal Commission for the Protection Against Sanitary Risks (COFEPRIS) and discuss at the San Diego meeting. FDA subject matter experts will participate in the meeting, and FDA will be involved in the ongoing activities of the USMBHC.

Finally, the Food Uniformity Act, if signed into law as currently written, would preempt a State of California food safety warning notification requirement unless it is an identical requirement, meaning substantially the same language as a comparable provision under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and that any differences in language do not result in the imposition of materially different requirements.

SCIENTIFIC INTEGRITY AT FDA

Question 2. It was a pleasure to work with you during your tenure at the National Cancer Institute. As you are aware in your new position at the Food and Drug Administration (FDA), there is a crisis of morale and adherence to science at the Agency. For example, according to a survey conducted by the Union of Concerned Scientists recently, a significant number of FDA professional staff and scientists responded that they have been asked "for nonscientific reasons, to inappropriately exclude or alter technical information or conclusions in a FDA scientific document" and that the public safety is not being adequately protected by the FDA, even within the Agency without fear of retaliation.

Are you concerned that hundreds of senior level scientists and professional staff at the Agency are reporting interference with their scientific work? Also, what do you propose to do to help restore confidence in scientific integrity within the FDA?

Answer 2. Senator, first and foremost, I am committed to ensuring FDA makes decisions based on sound science. I would like you to know that I will make myself personally available to staff who want to appeal decisions made by FDA management. I believe that the need to appeal to me will be rare, however, because I will ensure that there are strong policies and procedures in place for resolving issues involving dissenting opinions. Efforts toward that end will include promulgating new policies and procedures as necessary, and strengthening, by process improvement and best practices measures, many of those that are already in place.

For example, we are working to ensure a rigorous ombudsman program through which staff are welcome to promulgate dissenting opinions. Staff may also invoke

standard written procedures for facilitating and resolving differing professional opinions. In addition, our Center for Drug Evaluation and Research established a Drug Safety Oversight Board whose charter includes responsibility for deliberating on any dissenting opinions raised during evaluation of drug applications and surveillance of marketed products. Through these and other traditional management techniques, I believe we will successfully address any dissenting opinions, and I am committed to evaluating our processes and refining them as necessary to ensure that there is a healthy, open, unsuppressed scientific debate of issues at FDA.

Question 3. In further response to the Union of Concerned Scientists survey, scientists at every Center within FDA responded that they felt pressure to approve products within FDA despite concerns about safety. I urge you to review those statements carefully, as they include threats and bullying behavior that may be at the expense of the public's health.

In any quality organization, the goal is to seek continuous quality improvement and to constantly reassess one's practices, policies, and work. Unfortunately, the responses from FDA have, instead, in instances such as their response to Dr. David Graham's concerns about the safety of certain drugs, been dismissive of criticism or stated concerns and have largely ignored many of the serious problems that we have all witnessed with the FDA in the past few years.

What will you do to ensure a culture of openness so that management fosters an environment where scientific disagreements are acknowledged as being a necessary part of the scientific process and where science is not set aside for ideological purposes or due to industry pressure?

Answer 3. Please be assured that FDA is committed to providing an open and welcome culture for its employees and the vigorous scientific discourse that we rely on. As members of a scientific Agency composed of many scientific disciplines, FDA staff regularly engage in discussion, debate, and even disagreement on regulatory issues and FDA actions, much like the peer-review process used by scientists throughout the world. Such deliberation and disagreements are standard, expected, and wholeheartedly valued and encouraged by FDA management. They are a critical part of the process of scientific deliberation and discourse that is not unique to FDA—other Federal agencies operate this way, as do academic medical centers and institutes of higher learning, and many others.

FDA is as dedicated as ever to its time-honored tradition of encouraging vigorous debate among experts who use disciplined processes to arrive at consensus and conclusions. Data must be adequate and valid. Methods must be statistically valid and conclusions must be supported by facts. When FDA staff have serious scientific disagreements, the Agency has a formal scientific dispute resolution process that may be invoked to resolve disagreement.

Additionally, I want to assure you I, personally, am committed to ensuring FDA makes decisions based on sound science. I would like you to know that I will make myself personally available to staff who want to appeal decisions made by FDA management. I believe that the need to appeal to me will be rare, however, because I will ensure that there are strong policies and procedures in place for resolving issues involving dissenting opinions.

Many of these policies and procedures are already in place. For example, staff in our product Centers may seek help through their ombudsmen or by invoking written standard procedures for facilitating and resolving differing professional opinions. In addition, at the direction of the Secretary, FDA established a Drug Safety Oversight Board whose charter includes responsibility for deliberating on any dissenting opinions raised during evaluation of drug applications and surveillance of marketed products. Through these and other traditional management techniques, I believe we will successfully address any dissenting opinions, and I am committed to evaluating our processes and refining them as necessary to ensure that there is an open scientific debate of issues at FDA.

DRUG SAFETY

Question 4. Public confidence in the safety of prescription drugs and the process at the FDA has been fundamentally shaken in recent years. It's critical for the public health that we restore this confidence, but I'm very concerned that the scientists who are most familiar with the safety data on these drugs, and therefore in the best position to ensure that the drugs be labeled and made available in the safest possible manner, are being prevented from doing the part of their job that could make safer use of approved drugs possible. Over 80 percent of survey respondents to the Union of Concerned Scientists survey agreed that the "public would be better served if the independence and authority of FDA post-market safety systems were strengthened."

How will you ensure that the FDA staff responsible for monitoring the safety of drugs once they are on the market will have the independence within the Agency and the resources necessary to protect the public's health?

Answer 4. The decisionmaking processes at FDA incorporates science at all levels. FDA medical reviewers and scientists make regulatory judgments based on scientific data during both the drug review and post-market evaluation processes. The Agency makes, and will continue to make, these decisions in an open, transparent, and collaborative environment that offers several mechanisms for resolving differing scientific opinions. We weigh the scientific data regarding the inherent benefits of a product against its risks, and based upon the judgment of our medical reviewers, experts, and management about what that data tell us, we ultimately make a regulatory decision about that product. Over time, as the science underpinning our decisions changes and as we get new information regarding the basis and standards for our decisions, we move to re-visit our processes and respond to the new scientific information as appropriate and as necessary.

I am committed to continuing FDA's proud tradition of dedicated, highly qualified Agency employees, making science-based decisions to further our mission of protecting and promoting public health.

Question 5. In the Vioxx situation, FDA was expanding approval for Vioxx to juveniles at the very same time that Merck was rapidly moving in the opposite direction and withdrew the drug from the market just a month later. Paradoxically, Merck took an action through the withdrawal of Vioxx from the market in the interest of patient safety while FDA's last action was in the direct opposite direction.

What lessons has FDA learned from this experience and what steps are you taking to ensure that FDA is properly protecting the public's health, including juveniles, with respect to drug safety? What steps are you taking to ensure that the Office of Drug Safety (ODS) has more independence from the Office of New Drugs (OND) than currently is the case?

Answer 5. On August 19, 2004, we approved a supplemental application for the approval of Vioxx for the treatment of patients with juvenile rheumatoid arthritis (JRA), a chronic debilitating disease for which additional therapeutic options are needed. The approval decision was made taking into account the available data on the efficacy and safety of the drug as it was known at that time. Based on a careful review of those data, we concluded that the potential benefits of Vioxx outweighed the potential risks when used according to the approved labeling instructions. Subsequent to that approval, on September 27, 2004, Merck informed us of preliminary data from a large on-going study of Vioxx in the prevention of colon polyps in adults (the APPROVe trial), which showed an increased risk of serious cardiovascular adverse events in patients treated with Vioxx compared to placebo. Based on these new data, Merck voluntarily withdrew Vioxx from marketing worldwide on September 30, 2004. It was not possible for us to have considered the data from the APPROVe trial at the time the decision regarding approval of Vioxx for JRA was made because the data were not yet available.

We have always taken our responsibility for the protection of pubic health very seriously, and continue to do so. In recent years we have taken additional steps to further improve our review and oversight of safety information for approved drugs. For example, FDA has:

- Commissioned a study by the Institute of Medicine (IOM) to evaluate the entire current U.S. drug safety system, with an emphasis on the effectiveness of post-marketing surveillance;
- Implemented a formal program that fosters discussion and resolution of dissenting scientific opinions about drug safety as part of our decisionmaking during the product approval process;
- Conducted an open public hearing to solicit input from the public about our communications on drug safety concerns and held 31 advisory committee meetings (14 focused on risk or safety and 17 focused on the safety and efficacy of new drug applications) to discuss complex drug safety and risk management issues with foremost experts in the U.S. health care community;
- Established the Drug Safety Oversight Board to provide independent oversight and advice to the CDER's 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. I believe that the DSB continues to create a culture of openness and enhanced oversight around safety issues within CDER. During the past year, we have issued 16 Public Health Advisories about important drug safety issues. In 2005, the DSB, met 5 times and discussed critical safety issues;

• Published draft guidance about how we intend to increase the availability of the latest drug safety information to the public (FDA's "Drug Watch" for Emerging Drug Safety Information"). We are reviewing and addressing all submitted comments on the draft guidance and intends to issue a final guidance on disseminating emerging safety information.

• Awarded four contracts that give us access to databases containing pharmacoepidemiologic information. These data will be used to study the association of various medications with serious adverse effects; and

• Elevated the Office of Surveillance and Epidemiology (formerly the Office of Drug Safety) to report directly to CDER's Center Director and appointed an Associate Center Director for Safety Policy and Communication in order to sustain a multidisciplinary, cross-center approach to drug safety.

In addition, the Agency is working on:

• Improving our Adverse Events Reporting System (AERS), a computerized information database that supports our post-marketing safety surveillance; and

• Improving the Critical Path of Drug Discovery, a collaborative project designed to modernize drug development with the use of technologies such as pharmacogenomic tests and imaging techniques to assess the overall safety and effectiveness of new medicines.

With respect to a separate drug safety office, the nature of our knowledge of a drug's safety profile and the expertise required for the ongoing assessment of a drug's risk-benefit balance demand that these two activities be housed in a single center. Our knowledge of a drug's safety profile proceeds along a continuum, which begins with *in vitro* and animal studies (before the drug is ever administered to humans), continues to grow through rigorous clinical trials, and is further refined after a drug is marketed. It is the review and synthesis of this cumulative knowledge base that leads to the most accurate assessment of the drug's safety profile. In CDER, Office of New Drug (OND) staff is the most knowledgeable about the premarketing safety data, while Office of Surveillance and Epidemiology (OSE) staff specializes in the post-marketing safety issues. Staff from the OSE and OND work closely in the analysis of appropriate regulatory actions, together they take into consideration both risk and benefit information from pre-approval and post-approval sources. If pre-approval and post-approval functions were split, there would be a loss of continuity in the review of risks and benefits.

Additionally, separating these two activities into two centers would be very costly, because of the duplication of the wide range of expertise involved. Medical officers in OND whose areas of expertise include the affected patient population(s), medical conditions, and treatments, know the results of animal and clinical studies that supported approval of the product; in addition, they review studies with products that are used in the same patient populations, and products, some still in the investigational phase, from drugs in the same or related classes. This expert knowledge of the patients' medical conditions, availability of alternative therapies, and safety profiles from IND and NDA submissions is a crucial component in the review of newly identified risks and how they may impact benefits. OSE personnel provide expertise in the areas of epidemiological studies of large populations, evaluation of data from AERS (that is, spontaneous adverse event reporting) and large external data sets purchased for adverse event tracking and evaluation in specific populations, medication error prevention, and risk management techniques.

If the responsibilities were split into two centers, the safety center would have to duplicate the expertise of OND staff, with expert knowledge of patient populations, medical conditions, alternative therapies, and safety profiles from investigational new drug applications and studies in marketing applications to support approval to enable the safety center to make appropriate risk-benefit decisions and the drug approval center would have to duplicate the expertise of the OSE staff. Cross-center consultation would be much more difficult, and therefore, less efficient, than within center collaboration.

OND routinely meets with OSE staff to discuss the current or anticipated safety of marketed products. In addition, CDER has recently instituted safety meetings that are held periodically (monthly or bimonthly) to discuss new safety issues and the status of reviews and analysis of previously identified safety signals. Also, prior to approval of applications to market new molecular entities (NMEs), or nonNMEs, OND and OSE staff have pre-approval safety conferences. The OSE staff is also consulted by OND in many pre-approval activities that increase CDER's ability to understand and adequately monitor risk and benefit for marketed products such as medication error prevention and risk management plan review.

For the reasons mentioned previously—resources, communication, collaboration, leadership, and shared responsibilities—I do not believe that two separate and inde-

pendent centers would improve FDA's ability to fulfill its mission to protect the public health.

Question 6. What action has FDA taken since 2004 with respect to reassessment of the safety of Meridia, Crestor, Accutane, Bestra, and Serevent?

Answer 6. *Meridia (sibutramine hydrochloride monohydrate).*—We continue to receive 6-month safety assessments from the Data Safety Monitoring Board (DSMB) for the Sibutramine Cardiovascular Outcome Trial (SCOUT)—a large controlled trial examining the safety of sibutramine in obese patients at risk for cardiovascular disease. Thus far, the DSMB continues to recommend that the trial proceed as planned. On July 29, 2005, we approved a labeling supplement that incorporated additional information for patients with renal impairment or renal insufficiency.

Crestor (rosuvastatin calcium).—On March 2, 2005, we provided information about the risks associated with the use of Crestor via a Public Health Advisory, Press Release, Patient Information Sheet, and Healthcare Professional Sheet. In addition, the labeling for Crestor was revised to highlight important information on the safe use of Crestor to reduce the risk for serious muscle toxicity (myopathy/rhabdomyolysis), especially at the highest approved dose of 40 mg. The labeling was also revised to reflect the results of a large pharmacokinetic study involving a diverse population of Asian patients compared with a Caucasian control group that found drug levels to be elevated approximately twofold in the Asian population studied.

We continue to perform regular assessments of Crestor's safety, with a focus on kidney function and potential serious adverse effects on muscle through monitoring of adverse events from controlled trials and spontaneously submitted reports. We are also tracking the patterns of use of Crestor, in particular the 40 mg dose, through prescription use data.

Accutane (isotretinoin).—In July 2005, we provided information about potential risks (suicidal thoughts or actions) associated with the use of Accutane via Patient Information and Healthcare Professional Sheets. In addition, on August 12, 2005, we approved new labeling for Accutane including a strengthened risk management program, called iPLEDGE. The sponsors agreed to implement this risk management program that requires registration (in the iPLEDGE program) of wholesalers, prescribers, pharmacies, and patients who agree to accept specific responsibilities designed to minimize pregnancy exposures in order to distribute, prescribe, dispense and use Accutane. This information was relayed to consumers and healthcare professionals via a Public Health Advisory and Questions and Answers posted on our Website. On March 23, 2006, we posted information regarding the iPLEDGE program and frequently asked questions regarding this program. The iPLEDGE restricted distribution program was fully implemented in the first quarter of 2006. This unprecedented program has the full participation of all manufacturers of the drug, and requires that wholesalers, distributors, pharmacies, prescribers and patients participate in order to have access to the drug. FDA has worked extensively with the sponsors of the program, their contractor and the American Academy of Dermatology to ensure that iPLEDGE is implemented in a manner that maximizes safe use of isotretinoin, but still ensures that patients who need the medication have access to it.

Bextra (valdecoxib).—On April 7, 2005, we asked Pfizer to voluntarily remove Bextra from the U.S. market because we concluded that the overall risk versus benefit profile was unfavorable. Pfizer agreed to suspend sales and marketing of Bextra in the United States, pending further discussion with us. This conclusion was based on the potential increased risk for serious cardiovascular adverse events, an increased risk of serious skin reactions compared to other nonsteroidal anti-inflammatory (NSAIDs), and the fact that Bextra has not been shown to offer any unique advantages over the other available NSAIDs.

Serevent Diskus (salmeterol xinafoate).—On July 13, 2005, the Pulmonary-Allergy Drugs Advisory Committee held a public meeting to discuss the implications of recently available data related to the safety of long-acting betaagonist bronchodilators, including salmeterol. On November 18, 2005, we alerted healthcare professionals and patients that several long-acting bronchodilator medicines, including salmeterol, have been associated with possible increased risk of asthma-related deaths and worsening of asthma in some patients with asthma, and requested that manufacturers update warnings in their existing product labeling. On March 2, 2006, FDA approved new safety labeling and Medication Guides for patients for drugs containing salmeterol. There are two products containing salmeterol in the U.S. market: Serevent (salmeterol) and Advair (salmeterol and formoterol).

FDA ADVISORY COMMITTEES

Question 7. The FDA acted to remove Dr. Curt Furberg from a FDA advisory committee for alleged conflict of interest due to his citing concerns about a Pfizer drug. This is in contrast to the continued participation of numerous other advisory panel members who are linked in a positive manner to drug and device companies, report conflicts of interest, and have made statements in favor of the class of drugs being reviewed. It raises the question why industry critics appear to be held to a higher standard for removal than those who frequently consult for industry.

Recently, the deputy director of the FDA announced that the Agency will be redrawing its guidelines for staffing advisory committees. He said the Agency will make greater efforts to exclude scientists with conflicts of interest who currently get waivers to serve on these committees. He also suggested the process will become more open to outside participation and have increased transparency.

Could you please share with us the specifics in each of these areas: which conflicts of interest will still be eligible for waivers, and which will be grounds for automatic exclusion under the new guidelines? How will the Agency encourage greater public participation in the staffing of these committees? And how will it become more transparent? Will there be more consumer and ethicists represented on these advisory committees?

Answer 7. Dr. Curt Furberg was not removed from the COX-2 meeting in February 2005. Dr. Furberg participated fully in that meeting, consistent with applicable statutes, rules, and guidance regarding the evaluation and granting of conflict of interest waivers. We do not hold industry critics to a higher standard for removal than those who frequently consult for industry.

In a speech given July 24, 2006, Deputy Commissioner Dr. Gottlieb discussed efforts to revise guidelines detailing the kind of industry ties that are permitted for those who serve on our advisory committees (see *http://www.fda.gov/oc/speeches/2006/conference0724.html*). More specifically, we plan to revise the guidance documents used to determine how potential conflicts are evaluated, how waivers are granted, and how information regarding conflicts and waivers is disclosed. The goal is to make the process more transparent and clarify more of the case-by-case qualitative judgments we make when we evaluate each potential conflict. We do not plan to re-write existing rules, but instead to provide additional guidance and clarity regarding implementation of the existing statutory and regulatory framework regarding conflicts of interest. The revision process is currently underway and is a high FDA priority. We will make public the revised guidances as soon as they are completed.

We believe that these administrative changes will substantially improve the transparency of the process of managing our advisory committees, evaluating potential conflicts, and granting waivers where appropriate.

Question 8. In the Union of Concerned Scientists survey, one FDA scientist wrote about subtle ways that the FDA and applicants can manipulate the advisory committee process in favor of approval. He or she wrote that division directors can schedule committee meetings at inconvenient times to intentionally exclude certain members, that division directors and office directors can withhold damaging information from the Advisory Committee Briefing Document, and that management can "pressure reviewers to soften advisory committee presentations." He or she wrote that pharmaceutical companies hire as consultants as many scientists as possible with relevant expertise to render them ineligible for relevant committee meeting participation.

What will you do to mitigate these subtle but significant influences that bias the advisory committee process?

Answer 8. We are committed to an open and transparent advisory committee process that brings the best available scientific advice to the Agency in a public manner, consistent with relevant statutes and regulations. Our public meetings are open to anyone who wants to attend and anyone can ask questions. In these meetings FDA is put to the test, to explain and defend its scientific thinking in public. These public meetings are before a panel of experts with the breadth and depth of experience that enables them to dissect the results and to challenge our thinking. We believe that the best protection from undue influence is openness and transparency, which we are committed to provide.

FDA INTERVENTION IN PRE-EMPTION LAWSUITS

Question 9. FDA has intervened in cases on behalf of pharmaceutical companies claiming that FDA's authority preempted lawsuits in matters of drug safety. Lester Crawford, former FDA Commissioner, defended such actions by the FDA in a memo

he wrote on November 16, 2004, to all FDA employees announcing the resignation of Daniel Troy, Chief Counsel of FDA. He wrote,

> "Dan has also put his personal reputation on the line defending the Agency's prerogatives from intrusion by courts applying State law in product liability actions. I endorse this practice, and believe the policy is the correct one for the public health."

Rep. Maurice Hinchey called for Troy's resignation in July and noted Pfizer paid Troy's firm $358,000 for Troy's services on the company's behalf in 2001 just before he was hired at FDA. Then FDA spent 622 hours working on court briefings filed on behalf of drug manufacturers. As the wife of a man who committed suicide after taking an antidepressant drug said in a July 2004 *New York Times* article said,

> "I do not believe in frivolous lawsuits, but it's ridiculous that the government is filing legal briefs on the side of the drug companies when it's supposed to be protecting the public."

In light of all the other problems and lack of resources that FDA has to do its fundamental job, do you think that is an appropriate use of FDA's time and energy to file briefs in such cases on behalf of drug companies?

Answer 9. FDA's regulation of prescription drugs is designed to ensure each drug's optimal use through requiring scientifically substantiated warnings. Under the Federal Food, Drug, and Cosmetic Act, FDA is the public health agency charged with ensuring that drugs and devices are safe and effective, and that the labeling of drugs and devices adequately inform users of the risks and benefits of the product. FDA employs scientists and other experts who review the information submitted by the manufacturer on a product's risks and carefully titrate the warnings, etc. that should be placed on the labeling. FDA continuously works to evaluate the latest available scientific information to monitor the safety of products and to incorporate information into the product's labeling when appropriate. The public health risks associated with overwarning are as great as—if not greater than—the health risks associated with underwarning. Overwarning can cause patients not to take beneficial drugs and doctors not to prescribe them. Under-utilization of a drug based on dissemination of scientifically unsubstantiated warnings, so as to deprive patients of beneficial, possibly lifesaving treatment, could well frustrate the purposes of Federal regulation as much as over-utilization resulting from a failure to disclose a drug's scientifically demonstrable adverse effects. Further, allowing unsubstantiated warnings may also diminish the impact of valid warnings by creating an unnecessary distraction and making even valid warnings less credible. FDA considers itself to be the final arbiter of the content of drug and device labeling, and believes this is further substantiated by the courts in response to briefs filed by the Agency in support of preemption dating back to at least 1977.

With respect to the role of Mr. Troy at the FDA, I would have the following comment. It is my understanding, that upon joining the FDA, Mr. Troy consulted with agency ethics officials who worked with him to ensure that he was in compliance with all ethical requirements of Federal law, and he recused himself with respect to particular matters in which his former firm or former clients were a party or represented a party. Any allegations or suggestions that he did not conduct himself in compliance with applicable legal and ethical rules are false.

I believe that assisting the Department of Justice in cases in which the government believes that State law conflicts with the Federal Food, Drug, and Cosmetic Act (the act) is an appropriate use of FDA's resources. The Supremacy Clause of the U.S. Constitution mandates Federal preemption of State law in such cases. FDA has intervened to protect the public health by asserting its jurisdiction to make the final public health determinations for FDA-approved products.

To clarify, the Department of Justice has asserted Federal preemption in regard to drug labeling/advertising and device approvals/labeling in several court cases, often at the request of the courts themselves. In many cases, FDA used an implied conflict preemption analysis under the Supremacy Clause. FDA argued standard preemption principles that State law must yield to Federal law when application of State law makes it impossible to comply with both Federal and State law, or when State law acts as an obstacle to accomplishing Congress's objectives as expressed in the act. FDA believes that State law should not be used to second-guess its determinations, particularly where FDA reviewed the claims or warnings at issue, and rendered a judgment about whether they are false or misleading.

In the device context, FDA argued that State tort law claims are expressly preempted where FDA has approved an application for pre-market approval for a medical device, and further argued that Congress charged FDA with determining issues that the lower court in a specific case identified as issues for the jury. FDA asserted that State law should not be used to second-guess FDA's determination as to the

correct regulatory pathway for a medical device. In another case, FDA argued that Plaintiffs State tort law claims were expressly preempted by section 521(a) of the act, which preempts State device requirements that are different from or in addition to any requirement under the act.

OFF-LABEL DRUG USE

Question 10. The *Archives of Internal Medicine* recently published an article that estimated 21 percent of drugs are prescribed off-label and that, for about 73 percent of those prescriptions, there is little or no science to justify that prescription.

Could you describe what could be done to improve the quality of knowledge and safety about off-label use. For example, if the FDA determines that a drug is being heavily used off-label, could you require a company to conduct a post-market approval safety study?

Answer 10. Once a drug product has been approved by FDA for marketing for one indication, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling, i.e., for "off-label use." Physicians under their own responsibility may exercise judgment for the use of an approved drug for unlabeled indications when they are satisfied there is medical and scientific support that such use may benefit their patients.

The appropriateness of off-label use is highly variable, and it is difficult to evaluate. We routinely discuss post-marketing studies with companies and urge them to perform such studies regarding off-label uses when we believe it is appropriate. We monitor post-marketing safety information for all uses of every drug, whether they are approved and labeled or not, and take any necessary action to revise labeling based on the available scientific data, including data accumulated since the drugs were approved. There are examples in which labeling includes important safety information in populations for which the drug is not approved when it is known that the drug is used off-label in those populations. Regulations require a brief description of major limitations of use of a drug (for example, the lack of efficacy of the drug in particular subsets of the population).

GENERIC BIOLOGICS

Question 11. The European Union has moved to provide guidance on how generic biologics can be approved through a combination of nonclinical and clinical trials on a biologic-by-biologic basis. In the United States, other than one court-order approval, the FDA has not provided such guidance. Are you considering adopting an approach, such as the European Union approach, that will allow generic biologics to come to market and possibly result in billions of dollars of savings to consumers in the future?

Answer 11. FDA has determined that it would be appropriate to initially publish guidance that is more broadly applicable to follow-on protein products in general, rather than beginning with product-specific guidance. FDA expects that this approach will provide useful guidance to the industry, while ensuring that we do not stifle innovation and the utilization of state-of-the-art technologies. In addition, a sponsor may contact the Agency to request advice on a case-specific basis regarding the development of a follow-on protein product.

Even as guidance documents on follow-on protein products are being developed, the Agency has been moving forward with the review and approval of those follow-on protein products requlated as drugs for which the sponsors have met the statutory and regulatory approval requirements under section 505 of the FD&C Act. Most recently, we have approved Fortical (calcitonin salmon recombinant) Nasal Spray in August 2005, Hylenex (hyaluronidase recombinant human) in December 2005, and Omnitrope (somatropin [rDNA origin]) in May 2006.

It should be noted that currently there is no abbreviated approval pathway analogous to sections 505(b)(2) or 505(j) of the FD&C Act for several protein products for which the EMEA has provided guidance, as those products (recombinant human erythropoietin, recombinant interferon alpha, and recombinant human granulocyte-colony stimulating factor) are licensed under section 351 of the PHS Act.

RESPONSE TO QUESTIONS OF SENATOR MURRAY BY ANDREW C. VON ESCHENBACH

Question 1. In response to questions at the Senate HELP Committee nomination hearing, you responded to my question about your determination that 18 years of age was the appropriate age restriction for Plan B OTC. As I pointed out at the hearing, there seems to be a shift at FDA from 16 to 17 now 18 years of age. However, there does not appear to be any justification for this shift. Does the Agency have additional scientific data showing that young women under 18 could not use

Plan B safely and effectively as an OTC product? What information did you receive that resulted in your determination that 18 was the appropriate age? Did you consult with the original members of the FDA's Advisory Committee in reaching this decision or did you consult with health care providers that provide care to younger women?

Answer 1. I did not receive any additional scientific data nor did I consult an FDA Advisory Committee in reaching the decision that age 18 was the appropriate age. Dr. Galson, the Director of the Center for Drug Evaluation and Research, had previously concluded that the sponsor had not established that Plan B could be used safely and effectively without a prescription by young adolescents, women age 16 and younger (i.e., that it was appropriate for OTC use for women age 17 and older). In considering the difficulty of enforcing an age-based restriction on the availability of this oral hormonal contraceptive, I have concluded that 18 (rather than 17) is the more appropriate cutoff to best promote and protect the public health. The State-regulated pharmacies that will be dispensing Plan B® under Barr's voluntary Convenient Access, Responsible Education (CARE) program (as well as society as a whole) are more familiar with 18 as a cutoff age. I understand that in all 50 States, 18 is the age of majority (i.e., the legal delineation between minor and adult), and retail outlets, including pharmacies, are familiar with using 18 as the age of restriction for the sale of certain products. With regard to the sale of certain drug products, the legal age to purchase FDA-approved nonprescription nicotine replacement therapy products is 18. Moreover, I understand that as a matter of State law, many products routinely sold by pharmacies, e.g., tobacco products and nonprescription cough-cold products like pseudoephedrine are restricted to consumers 18 and older. The approach builds on well-established State and private sector infrastructures to restrict certain products to consumers 18 and older. This approach should, therefore, help ensure safe and effective use of Plan B.

Question 2. Based on FDA's decision to place an age restriction on an OTC product due to safety, can we assume that all OTC applications will be considered under these circumstances? I know that the Agency is currently reviewing a weight loss medication OTC application. Will FDA be requesting data on the safety of this product for younger patients? Will FDA be reviewing this application to determine how this product may affect behavior? And, finally will FDA be asking the manufacturer how to ensure that this medication can be taken safely without a physician's supervision?

Answer 2. In any request to switch a prescription product to OTC status, FDA applies the statutory standard and considers available data to determine whether prescription dispensing is "not necessary" for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and . . . the drug is safe and effective for use in self-medication as directed in proposed labeling.

Such switch applications generally include data from actual use and labeling comprehension studies to demonstrate that the product can be safely and effectively used without the supervision of a practitioner licensed by law to administer the drug. FDA may approve an NDA application only when, among other things, the investigations submitted in the application include adequate tests showing whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling and when there is sufficient information to determine from the application whether the drug is safe for use. FDA will apply these statutory standards to any switch application submitted to it.

Furthermore, Dr. Galson, the Director, Center for Drug Evaluation and Research, has indicated that he intends to work with FDA's scientific staff to initiate a process to further develop the Agency's understanding about pediatric use of OTC drugs. One of the questions he intends to address will be how to establish the data requirements regarding use patterns in these special age groups in which age is not merely a chronologic deterrent, but also a biologic deterrent.

Question 3. When FDA approved the original Plan B application for prescription in 1999 as an emergency contraceptive, did the Agency request additional data on younger women? Was there a distinction made between the safety and efficacy for women over 18 and women under 18? Was the issue or concern about behavior part of the approval process?

Answer 3. FDA did not request additional data on younger women as part of the original approval process for Plan B as a prescription product. Prescription Plan B was reviewed in a manner similar to that for all hormonal contraceptives. Prescription oral contraceptives have been determined to be safe and effective, for all women after they have passed through menarche and are having menstrual cycles, when

used following the direction of a healthcare provider. The issue or concern about age was not a significant consideration during the original approval process for prescription Plan B since woman could only obtain the product with a prescription from a healthcare provider. The issue regarding additional data for younger women arose in the sponsor's actual use and labeling comprehension studies submitted to support the switch to OTC, not in the original prescription application.

Question 4a. In the announcement of July 31, 2006, FDA indicated that they would be working with the manufacturer of Plan B to determine appropriate enforcement mechanisms for ensuring that women under 18 did not receive the product as an OTC. How does FDA currently enforce risk management responsibilities?

Answer 4a. For prescription Plan B, there are no special procedures or responsibilities beyond those normally required for all prescription drug products. In this case, the company proposed to market prescription Plan B and nonprescription Plan B in the same box. Therefore, certain marketing restrictions are appropriate to ensure that Plan B is made available to one population on a prescription basis and another population on a nonprescription basis. Both FDA and manufacturers are involved in ensuring that restrictions on distribution and use are followed. Manufacturers typically submit, as part of their application, a plan to address any marketing restrictions, which often includes, as here, education and monitoring. Enforcement of risk management responsibilities for other products varies depending on the specific drug product.

Question 4b. As I mentioned at the hearing Accutane has a number of label safety restrictions for women due to the documented risk of miscarriage and birth defects. Women have to prove that they are in fact not pregnant and they are currently using two forms of birth control. How does FDA ensure that women under 18 are able to comprehend this labeling restriction and effectively use 2 forms of birth control? I realize this is a prescription medication, but it is taken every day without physician supervision.

Answer 4b. The sponsor's iPLEDGE program for Accutane is aimed at preventing use of the drug during pregnancy. To obtain the drug, in addition to registering with iPLEDGE, patients must comply with a number of key requirements that include completing an informed consent form, obtaining counseling about the risks and requirements for safe use of the drug, and, for women of childbearing age, complying with necessary pregnancy testing. Prescribing physicians, responsible for administering the informed consent, are also responsible for judging their patients' comprehension of the restrictions.

To convey important information about risk-reduction to women of child-bearing potential, iPLEDGE provides the following education materials: the iPLEDGE Patient Introductory Information Brochure, the iPLEDGE Program Isotretinoin Educational Kit for Female Patients who Can Get Pregnant (which includes the Guide to Isotretinoin for Female Patients Who Can Get Pregnant, Birth Control Workbook, Contraception Referral Form and Contraception Counseling Guide, Patient Identification Card, Patient Information and Informed Consent form, and Patient Flowchart), and a Medication Guide.

In addition, the patient, in interacting with the iPLEDGE system, is queried to ensure her understanding of the risks of the drug and the importance of using effective contraception. If there is any suggestion that she does not have a complete understanding, she is not cleared for dispensing of isotretinoin through the system, but is instead referred back to her physician.

Question 4c. Finally, would Plan B be recommended for women taking this medication as a method of birth control?

Answer 4c. Plan B should not be used as one of the 2 forms of birth control recommended for users of Accutane. Plan B is not approved for routine contraception use. It is only approved for emergency use. Labeling for Plan B (both nonprescription and prescription) does/will not recommend the use of Plan B in conjunction with Accutane.

Question 5a. One of my major concerns about the Plan B OTC application process has been the appearance that political forces, not science have dictated this process. Have you discussed this process or your July 31st announcement with individuals at the White House?

Answer 5a. I have never discussed the Plan B application process with anyone at the White House.

Question 5b. How many current applications at FDA from drug approvals to medical devices to OTC applications do you personally decide? What is the percentage

of decisions issued by FDA regarding food safety, drugs or devices that you personally sign?

Answer 5b. Under the act, the authority to approve drug and device applications is specifically assigned to the Secretary of Health and Human Services. That authority, in turn, has been delegated to the Commissioner of the FDA and redelegated to the Directors of CDER, CBER, and CDRH. Therefore, it is appropriate for a Commissioner to directly act on a drug or device application. That said, the decision to approve Barr's supplemental new drug application for Plan B was made by CDER. Prior to the Center's decision on the application, I determined that further rulemaking by the Agency was not required to address the unique regulatory issues related to this particular application. I determined this was an appropriate resolution to the Advance Notice of Proposed Rulemaking (ANPRM) process that was put in place by my predecessor. I also determined that 18 was the appropriate age to enforce the partial OTC switch requested by Barr. While I am unaware of any pending applications on which I would make decisions regarding approval, it is customary for a Commissioner to be briefed and updated on high-profile decisions before the Agency, and to exercise his/her authorities when appropriate.

Question 5c. And, finally it has come to my attention that there are a large number of political appointees now serving the Commissioner's office. Can you please provide to me the current number of political appointees within the FDA and does this number represent an increase or decrease from past Administrations?

Answer 5c. Of the more than 10,000 FDA employees, only five are political appointees, including myself. It is my understanding that this number is generally consistent with past Administrations.

Question 6. In 2002 and 2003 when we enacted the MDUFMA and the technical corrections legislation, I was very interested in the need to provide additional incentives to improve pediatric labeling of medical devices. As a strong supporter of the Better Pharmaceuticals Act for Children and the FDA Pediatric Rule, I believe we can provide incentives to encourage manufacturers to seek on label approval for pediatric drugs and devices. However, the task of determining the appropriate mechanism for medical devices has proven to be difficult. I recognize the differences between drugs and devices but I do believe we can do more to address this inequity. I would be interested in your insights as a practitioner and as the Acting Commissioner on what steps we can take to ensure greater pediatric labeling of medical devices.

Answer 6. Labeling devices for pediatric use is of significant interest to FDA, and the Center for Devices and Radiological Health (CDRH) has taken important steps to ensure that devices have pediatric labeling, as needed. It is important to note, however, that although some medical devices are specifically designed for use on infants and children, such as infant incubators and infant radiant warmers, the majority of devices going to market are indicated for the general population. As such, although the labeling does not indicate the device for pediatric use, it does not exclude such use. Because these devices can be used in both the pediatric and adult populations, they are not specifically labeled as pediatric devices.

There are many challenges influencing the development of pediatric devices. Due to natural growth and development of a child, long-term or permanent implants would need to "grow" with the subject or at least remain functional while the child develops. Because of the young age of the patients, the devices would also need to have a longer life span. In general, the smaller size of children requires smaller devices, oftentimes requiring that the entire product would need to be re-engineered to ensure that the functionality remains consistent when the size changes or as the child grows.

To address these issues, CDRH has taken a number of important initial steps. These include: (1) a guidance for pediatric devices which identifies the types of information needed to support marketing and discusses labeling issues for pediatric devices (cite to name of guidance—"Pre-market Assessment of Pediatric Medical Devices—Guidance for Industry and FDA Staff"), (2) encouraging sponsors to consider pediatric populations during meetings where trial designs and indications for use are discussed, and (3) instituting a policy to encourage the discussion of pediatric issues at Advisory Committee meetings.

Recently, CDRH formed a pediatric steering committee (SC) to oversee pediatric issues throughout the Center. Its functions include facilitating and encouraging pediatric pre-market reviews and consults. The SC has also set up a process to allow the Center to track pediatric PMAs and HDEs (Humanitarian Device Exemptions) and has developed a checklist to be used during the review of pediatric study protocols to ensure key information is captured.

MDUFMA allows for a user fee exemption for device submissions solely for pediatric use. This is intended to encourage pediatric device development. In addition, HDEs do not require a user fee, and several products specifically for use in pediatrics, including life-saving cardiovascular technologies, have been approved as HDEs.

CDRH hopes that through a combination of greater awareness of the medical need, more open interactions with industry and pediatric societies, and minimizing financial burdens to manufacturers, the Agency can help ensure greater interest in pediatric labeling of medical devices.

Question 7. When we look toward reauthorization of the PDUFA, one of the areas that I would like to see modernized is the issue of clinical trials. For many orphan or rare diseases or even some pediatric diseases, it is very difficult to meet the current threshold for clinical trials. I realize that the Agency has an obligation to protect patients but many times it is difficult to conduct a broad-based clinical trial as the population is too small or the costs too great. Is there a way that we can use new technology to address this concern without jeopardizing patient safety?

Answer 7. We think that new bioinformatic technologies, particularly model-based product development, hold potential to transform clinical trial design. In the Critical Path Opportunities Report and List, which we published in March 2006, we note that many rare diseases are hard to study due to the difficulty of enrolling subjects, and note the potential that databases recording the natural history of patients with rare diseases, incorporating observations of clinical progression and biomarkers could assist in creating disease models to support better designed clinical programs. No one company, university, or governmental agency has the necessary information to create computer models sufficiently robust to accomplish these and other goals. The effort will require new strategies for information sharing and safe information housing, and a commitment to collaborative approaches. FDA is actively considering, under the Critical Path initiative, a variety of study designs, methods of analysis and uses of data from other studies to improve decisionmaking and the rate of success of studies. We continuously evaluate new clinical trial designs that hold the promise of more efficient drug development as well as nontraditional statistical approaches that may lead to more efficient drug development. For example, the appropriate use and applicability of historical controls in which the effect of a new treatment in a group of patients is compared to well-documented experience from other studies is considered in detail in the International Conference on Harmonization (ICH) guidance E–10 (Choice of Control Group and Related Issues in Clinical Trials.), and in certain circumstances such trials designs are employed to expedite drug development.

Under certain circumstances, we also have the authority to base a finding of substantial evidence of effectiveness on the results of a single adequate and well controlled clinical study rather than the more traditional two-study standard. This standard can help speed important new therapies to market by reducing the number of trials that must be performed to gain marketing approval. Also, under certain circumstances, we can approve drugs on the basis of their effects on a marker that is reasonably likely to predict a clinical benefit, provided that we are able to obtain evidence after approval to establish that the drug had clinical benefit. This approach is reserved for serious or life-threatening illnesses for which there are inadequate available treatments. Although there are difficulties with this approach and it must be used with caution, where appropriate, it can drastically reduce the time to market for important new drugs.

Question 8. While both drugs and medical devices are used to diagnose and treat human illness, there are significant differences between the two categories of FDA-regulated products recognized by Congress in their respective statutory frameworks. Will you continue to treat medical device issues on their own merits and tailor medical device policies to recognize their unique features and unique role in medical practice?

Answer 8. FDA recognizes that there are important inherent differences between drugs and devices and these differences require unique regulatory approaches.

Whereas small changes in a drug compound can often have profound effects on its mechanism of action and therefore the product's safety and effectiveness, minor changes in devices can often be made without greatly altering the function of the device. CDRH's 510(k) premarket notification regulations for lower risk devices allow many products which are "substantially equivalent" to existing, legally marketed devices, to reach the marketplace in an efficient manner, for example, based on pre-clinical bench and/or animal data alone. Every year CDRH clears thousands of new devices through this less-burdensome mechanism. FDA has also succeeded

in applying the appropriate level of regulatory controls to assure the safety and effectiveness of combination products where there is a merging of devices and drugs.

How devices are used also requires us to tailor device-specific policies. For example, most drugs are administered orally or intravenously and a placebo is often indistinguishable to the patient and/or clinician in a clinical trial. However, devices often require surgical implantation or cause a physical reaction to the body which a patient and physician would be well aware of. In addition, device use (and hence safety and effectiveness) can often be affected by the experience and skill level of the user. These and other issues make device trial design and data interpretation especially challenging.

We also recognize the financial burden on sponsors when clinical trials require expensive operations or where the nature of the device requires particularly long follow-up. FDA's regulations and policies allow us to take these issues into consideration by providing ample latitude in defining what constitutes "valid scientific evidence."

In summary, our current device classification system allows us to apply different policies and regulations to products depending on their associated risk and/or equivalence to other similar products in a least burdensome way, thus enabling FDA to address the unique issues associated with medical devices.

Question 9. The FDA's Critical Path Initiative has potential to improve the development process for medical technologies and bring better devices to market faster. Yet most of FDA's projects under the Critical Path initiative are focused on drugs—very few are dedicated to medical technology development. Given that the device development process for drugs and devices are vastly different, will you work to ensure the Agency dedicates more projects to device issues?

Answer 9. Device sciences are front and center in FDA's Critical Path Initiative; however, I would caution against a narrow view of which projects will help improve device development. The List is divided into six priority areas, rather than into product types, because these priorities—and many of these projects—apply across product areas and will require collaboration among experts in the development of drugs, devices, and biologics in order to succeed. For example, work to improve clinical trial design or to develop a robust clinical bioinformatics infrastructure will improve development of all medical products. Similarly, the full potential of genomic biomarkers cannot be achieved without new approaches not only to development of the drug or biologic therapy, but also to development of the partner in vitro diagnostic device needed to identify the presence or absence of the biomarker in an individual.

The release of the list marks a starting point in identifying priorities to be accomplished under the Critical Path Initiative. It is meant to spur a continued discussion among industry, academia, patient and professional groups and government organizations about the research priorities that need to be accomplished in our effort to modernize the medical product development process. The List was compiled from ideas we received during nearly 2 years of outreach, including an open public docket and meetings with companies and trade associations. Device interests were well represented. We look forward to additional input from device interests.

Question 10. Women and other minorities have consistently been under-represented in clinical trials, causing most of the assumptions about a drug's effectiveness and side-effect profile to be based on predominate experience in men. Given the recent biologic evidence that gender may be important in determining a drug's effectiveness and/or side-effect profile, the committee would appreciate your comments on whether the FDA should require—or at the very least encourage—the exploration of gender differences in clinical trials and the drug approval process.

Answer 10. We are continuing to meet and work with various groups to encourage sponsors to study and report the effects of drugs in a population that is representative of the population the drugs will be used in, including men and women. To this end, we finalized a guidance to recommend categories for collecting data regarding race and ethnicity ("A Guidance for Industry—Collection of Race and Ethnicity Data in Clinical Trials,") in September 2005. A copy can be found at: *//www.fda.gov/cder/guidance/5656fnl.pdf.*

On July 22, 1993, we also published the "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs" that explicitly describes our expectation that women should be included in all phases of drug development. Current regulations permit the Agency to prevent a clinical trial from proceeding if ". . . men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk . . . of reproductive toxicity." See 21 CFR 312.42. This reflects the Agency's view that

women should not be excluded from clinical trials simply because they are biologically capable of becoming pregnant (women who are pregnant are not covered by this regulation). In addition, the Agency is developing a model and protocol standards that would allow gender, age, and race to be captured as demographic variables and enhance Agency monitoring of participation based on these characteristics from clinical trial data submissions. We will consider other guidance and initiatives as the need becomes apparent.

Question 11. Given the FDA's acknowledged support for the concept of personalized medicine, is it your view, as the head of the FDA, that gender-based medicine should be included within that concept?

Answer 11. Yes. Personalized medicine requires the assumption that parameters measured for an individual, including information associated with his or her genome, can accurately predict therapeutic response. Gender-based medicine is part of personalized medicine. For example, only 20–25 percent of women with breast cancer have tumors that over-express HER2 and thus would be good candidates for herceptin therapy. Treating women with herceptin based only on their gender would result in no benefit to the subset of women (75–80 percent) whose tumors do not over-express HER2. However, with a greater understanding of the molecular basis of disease and drug response than we have today, we can do better. Thus, the FDA's commitment and support for personalized medicine is to go beyond gender and race. FDA is working to facilitate development of genomic tools that can increase the precision by which personalized medicine can be delivered to patients to improve the overall benefit/risk profile of drug treatments.

It is important that these considerations continue to be included in our agency-wide efforts to bring personalized medicine to consumers. The FDA has a dedicated office, the Office of Women's Health, addressing questions specifically related to gender-based medicine. This office is working closely with other parts of the FDA on a number of projects that will help us to better understand, and take action on, issues related to gender-based differences in drug response.

Question 12. The issue of gender bias in research is one that FDA needs to be vigilant in addressing. I applaud the steps taken by both FDA and NIH in working to eliminate gender bias in research and development of new therapies. However, much more needs to be done that new drug therapies are properly labeled for women. I am also very concerned about the impact of an expedited FDA approval process as envisioned under Bioshield. I realize that getting new life saving vaccines and antivirals is critical in preparing for a pandemic or bioterrorist attack, but we must also ensure that these treatments are in fact safe. FDA must ensure that special populations like women, pregnant women and children are not forgotten. It's essential that any review process for new vaccines or antivirals include data on safety for these populations. Can you provide to me the measures you have taken to ensure that at-risk or special populations are part of the FDA approval process for new vaccines and drug treatments to protect against a pandemic or bioterrorist attack?

Answer 12. Attention to potential gender, age, racial and ethnic differences in response to medical products is part of a larger effort by the FDA to ensure that the safety and efficacy of medical products are adequately studied in people who represent the full range of patients who will receive the products after approval. Our regulations and guidance encourage the participation of women and individuals from underrepresented racial and ethnic groups in all phases of product development. FDA also promotes collection of gender, age, and race-related data during research and development, and recommends analysis of the data for demographic effects.

These principles also apply to FDA's efforts to facilitate the development and availability of safe and effective medical countermeasures against threat agents. The legal standards for product approval, licensure, and clearance under the Federal Food, Drug, and Cosmetic Act (the act) and the Public Health Service Act apply equally to countermeasures and to other medical products. Recent legislation has established an authority to allow temporary access to unapproved medical countermeasures during an emergency. Specifically, the Project BioShield Act of 2004 authorizes the use of certain unapproved medical products or unapproved uses of approved medical products during declared emergencies. Before the Commissioner can issue an Emergency Use Authorization (EUA) for a particular product, the HHS Secretary must first declare that the emergency justifies issuance of an authorization. Moreover, the Commissioner must determine that the product meets the statutory criteria for issuance, which include a consideration of whether the known and potential benefits of the use outweigh the known and potential risks of the product.

The determination of risks and benefits is a product-specific and circumstance-dependant analysis that may involve a number of factors, including the needs of special populations.

RESPONSE TO QUESTIONS OF SENATOR REED BY ANDREW C. VON ESCHENBACH

Question 1a. Dr. Von Eschenbach, last fall you reconvened the Counterfeit Drug Task Force to examine the progress that has been made in the adoption of electronic tracking technology, commonly referred to as radio frequency identification (RFID), to protect the integrity of our drug supply. Like you, I am alarmed by the proliferation of increasingly sophisticated counterfeit medications that are finding their way to the marketplace. However, I am also concerned about the slow pace of implementation of this tracking technology as well as the fact that FDA has not utilized authority under the Prescription Drug Marketing Act (PDMA) to push manufacturers and distributors to accelerate its deployment. What prompted you to reconvene the task force?

Answer 1a. As FDA continued to monitor the adoption and implementation of e-pedigree and electronic track and trace technology, we recognized that adoption across the U.S. drug supply chain was slower than originally anticipated, so we reconvened the task force to evaluate appropriate steps to take.

Question 1b. Could you please comment on the findings of the task force?

Answer 1b. In June 2006, in its Counterfeit Drug Task Force Report—2006 Update, FDA announced new steps to strengthen existing protections against the growing problem of counterfeit drugs. The measures emphasize certain regulatory actions and the use of new technologies for safeguarding the integrity of the U.S. drug supply.

Among other new measures, FDA will fully implement regulations related to the Prescription Drug Marketing Act of 1987, which requires drug distributors to provide documentation of the chain of custody of drug products (a pedigree) throughout the distribution system. A potential new measure to safeguard the drug supply is the use of electronic track and trace technology, such as radio-frequency identification (RFID), which creates an electronic pedigree (e-pedigree) for tracking the movement of the drug through the supply chain. FDA had expected this technology to be in widespread use in the drug supply chain by 2007. In early 2004 FDA delayed the effective date of the regulatory provisions regarding pedigrees to allow the industry time to adopt this technology. However, it now appears that FDA's expectations for adoption of the technology by 2007 will not be met. FDA therefore has determined it can no longer justify delaying implementation of the pedigree regulations.

FDA also announced that, during the next year, its enforcement of the pedigree regulations will focus on products most susceptible to counterfeiting and diversion. FDA announced in the *Federal Register* the availability of a draft compliance policy guide (CPG) for public comment describing this enforcement approach.

The Task Force report also underlines FDA's belief that widespread use of e-pedigrees using electronic track and trace technology, including RFID, would provide an electronic safety net for our Nation's drug supply. The report therefore recommends that stakeholders continue to work expeditiously toward that goal, and that their implementation of RFID technology be used first on products most susceptible to counterfeiting and diversion.

Additional topics discussed in the Task Force's report include the following key issues related to electronic track-and-trace that are in need of resolution:

- Technical aspects of the mass serialization of marketed drugs by assigning a unique identifier or serial number to each drug package as the initial step in development of track and trace technology.
- Protection of consumer privacy to prevent unauthorized disclosure of information stored in RFID tags when RFID-tagged drug products are dispensed to consumers.
- Consumer education about RFID and the labeling of RFID-tagged drug products, to disclose to consumers when they are receiving RFID-tagged products and to inform consumers of the benefits of RFID technology and how consumers' privacy is being protected.

Question 1c. Should you become commissioner, would you exercise the authority under PDMA to ensure the integrity of our domestic drug supply?

Answer 1c. We will continue to use all of the authority that Congress has granted FDA to ensure the integrity of our domestic drug supply. As we noted in our statements, FDA will no longer delay the effective date of the pedigree regulations and

has published a draft CPG that describes our enforcement approach. Further, FDA's Office of Criminal Investigations (OCT) has been pursuing violations of the PDMA since OCI's inception and will continue to do so.

CITIZENS PETITIONS AND THE DELAY OF GENERIC COMPETITION

Question 2a. FDA regulations permit any interested person to file a citizen petition requesting FDA "to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action" (Title 21, Code of Federal Regulations 10.25 and 10.30). Citizen petitions may be submitted at any time. I understand that the backlog of citizen petitions has grown in recent years, particularly as they pertain to generic drugs. It has been reported that these requests for agency action are being misused by brand-name drug manufacturers to stave off generic competition.

Could you please tell the committee what increases the FDA has seen in the number of citizen petitions that have been filed in recent years, and what the Agency is doing to work through the growing backlog?

Answer 2a. The Center for Drug Evaluation and Research (CDER) is responsible for responding to citizen petitions relating to certain drug products, including generic drugs. Within CDER, the Office of Regulatory Policy (ORP) has primary responsibility for drafting responses to citizen petitions, except for petitions relating to over-the-counter drug monographs or "suitability" petitions (see 21 CFR 314.93). Recently, CDER has seen a significant increase in petitions. For example, ORP saw a 50 percent increase in petitions received in calendar year 2004 over calendar year 2003. ORP received 70 citizen petitions in 2004, and 65 in 2005. For calendar year 2006, we anticipate a greater increase because ORP has already received 53 petitions as of July 31, 2006. This increase includes not only citizen petitions relating to Abbreviated New Drug Applications (ANDAs) or generic drug applications, but also an increasing number of petitions raising drug safety issues.

In response to the increase in petitions and an increasing backlog of pending petitions, ORP initiated an extensive review of processes for responding to petitions. As a result, CDER instituted a number of changes, including:

- ORP has been increasing its early interactions with other offices to better coordinate responses.
- All parties involved in responding to petitions have attempted to increase communications to avoid misunderstandings, wasted efforts, or unnecessary delays.
- ORP and the Office of Generic Drugs (OGD) regularly discuss priorities and anticipated timetables, so responses can be coordinated with ANDA approval actions.

In addition, OGD has made organizational changes to improve the petition response process. OGD has dedicated a group of highly skilled scientists to address complex scientific issues related to review of ANDAs and citizen petitions. This change is expected to increase the consistency, quality and speed of OGD's input on petition responses.

Question 2b. Similarly, what is the FDA doing to address the allegation that brand name drugmakers are using the citizen petition process to delay the introduction of generic products?

Answer 2b. With respect to allegations that petitions are used to delay competition, FDA plans to review petitions from innovator and generic drug manufacturers that have been denied. We will consider such factors as the timing of the petition and the nature and age of the data supporting the petition. Should we believe that further investigation into potentially anti-competitive behavior may be warranted, we intend to refer the cases to the Federal Trade Commission.

UVA/UVB LABELING FOR SUNSCREEN

Question 3. The fiscal year 2006 Agriculture Appropriations conference report included language directing the FDA to complete the sunscreen monograph, which will guide UVA and UVB labeling information for over-the-counter (OTC) sunscreen products, within 6 months of passage of the agriculture appropriations bill. That bill was signed into law on November 10, 2005. We are now approaching 3 months that this provision is past due and still no sunscreen monograph. The FDA began drafting a monograph for sunscreen products in 1978 and has yet to complete it. Please provide the committee with the following information:

(a) an accurate time-line detailing a plan of action for completing the monograph;
(b) any perceived or acknowledged obstacles to completing the monograph by the end of calendar year 2006; and
(c) an explanation as to why the monograph has not been completed.

Answer 3. It is anticipated that a rulemaking will be issued by the end of calendar year 2006 to propose new testing and labeling, primarily for products that contain ingredients that block UVA rays. FDA drafted this proposed rule after asking for comments specific to this topic in a June 2000 *Federal Register* notice. As the Agency developed the rule new issues emerged that needed to be addressed. For example, recently FDA received a citizen petition requesting that the Agency amend the OTC sunscreen drug monograph to consider OTC sunscreen drug products containing nanoparticles as not covered under the monograph and instead treat them as new drugs. The proposed rule is currently in clearance.

The period for public posting of comments associated with the proposed rulemaking, once published, is 90 days and FDA will subsequently issue a Final Rule. The time to publication of the final rule is dependent on the number and content of the comments submitted in response to the proposed rule and the Agency's clearance process.

Question 4. Similarly, the current FDA-mandated warning label on indoor tanning equipment has not been updated since 1979. Yet, the Department of Health and Human Services (HHS) has declared UV radiation, including that which is emitted by indoor tanning devices, as a known carcinogen. The FDA claims the delay in updating the label is due to the need to harmonize the label with international standards. In the mean time, on average more than one million people visit tanning salons every day with 30 million people tanning indoors in the United States each year. Of those 30 million, 2.3 million are teens. The World Health Organization has even suggested a ban on minors accessing this equipment.

Where do revisions to the current label stand and what is the Agency's time-line for making the new label available for public comment?

Answer 4. Sunlamp products are Class I medical devices, classified as ultraviolet lamps for tanning. They are subject to the general controls for medical devices, including registration/listing and quality system regulation requirements. They also are subject to the electronic products performance standard for sunlamp products (21 CFR 1040.20). The current FDA warning statement required on sunlamps (tanning beds and tanning booths) and in their user instructions is as follows:

> "DANGER—Ultraviolet radiation. Follow instructions. Avoid overexposure. As with natural sunlight, overexposure can cause eye and skin injury and allergic reactions. Repeated exposure may cause premature aging of the skin and skin cancer. WEAR PROTECTIVE EYEWEAR; FAILURE TO MAY RESULT IN SEVERE BURNS OR LONG-TERM INJURY TO THE EYES. Medications or cosmetics may increase your sensitivity to the ultraviolet radiation. Consult physician before using sunlamp if you are using medications or have a history of skin problems or believe yourself especially sensitive to sunlight. If you do not tan in the sun, you are unlikely to tan from the use of this product."

The purpose of the warning statement is to provide information necessary for consumers to make an informed decision regarding the risks of using sunlamp products. The warning statement must be legible and readily accessible to view by the person being exposed immediately before use of the product.

FDA staff have worked closely with the International Electrotechnical Commission (IEC) to amend the IEC standard for "Household and similar electrical appliances—particular requirements for appliances for skin exposure to ultraviolet and infrared radiation products." Amendment 2 is scheduled for the Final Draft International Standard (FDIS) stage in August 2006.

The FDA intends to consider whether amendments to the performance standard for sunlamp products should be undertaken to achieve closer agreement with the IEC standards. Any proposal initiated would likely include proposed changes to the required warning statement to improve readability and to increase the likelihood that the warning will reach consumers.

SAFETY OF FLU VACCINES

Question 5. A couple of years ago, FDA inspectors discovered manufacturing problems at the Liverpool vaccine facility of Chiron. Yet, these problems did not become public until several months later when the British government declared 40 million doses of the vaccine unusable just prior to the start of flu season. This announcement left many States without adequate supplies for the season and left many questioning FDA's ability to respond swiftly and effectively to problems that may arise during annual flu vaccine production.

What steps has FDA taken to ensure that this level of communication breakdown doesn't happen again? Why did it come down to the British government barring the shipment of the contaminated vaccine and not the FDA?

Answer 5. The Agency has made significant changes to address a number of issues. For example, FDA now conducts inspections of influenza vaccine manufacturers on an annual basis. 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 U.K. Medicines and Healthcare Products Regulatory Agency (MHRA) that covers exchange of information for all inspections.

RESPONSE TO QUESTIONS OF SENATOR CLINTON BY ANDREW C. VON ESCHENBACH

Question 1. Dr. von Eschenbach, as you know, the FDA has had this application for over 3 years—since April 21, 2003—and we appear to be no closer to having a resolution than we were the day it was filed. We had a promise from Secretary Leavitt that we would have a decision on this application by September 1st and today, almost an entire year later, we are still waiting. We have been clear all along that we are not asking for a specific outcome—we are simply asking for a decision. When are we going to have a decision from the FDA?

Answer 1. On August 24, 2006, FDA approved the amended sNDA from Barr Laboratories allowing OTC sale of Plan B® to adults 18 and older. Plan B will be available to patients 17 and younger by prescription.

Question 2a. In your letter to Mr. Carrado, you also discuss the CARE$^{\Sigma M}$ Program, a program proposed by Duramed outlining the marketing, education, distribution, and monitoring for the OTC version of Plan B. Specifically, you express the FDA's strong interest in Duramed's enforcement strategy if a pharmacy fails to comply with regulations to keep Plan B behind the counter and to require that patients show photo identification to obtain the drug. Is it considered standard procedure to hold pharmaceutical companies liable for the actions of independent pharmacies?

Answer 2a. The approval of Plan B does not hold Duramed liable for the actions of independent pharmacies. Duramed provided revisions to its CARE$^{\Sigma M}$ program that satisfied FDA that it would take steps to monitor the implementation of the program and report to FDA periodically regarding the results of its monitoring program. The program also provides that the sponsor will report repeat violators of the age restriction to the appropriate State Boards of Pharmacy. FDA intends to monitor the program's effectiveness so that we can discuss with the sponsor further modifications, if necessary, to prevent inappropriate use of Plan B.

Question 2b. Later on in your letter, you write,

> "If after our discussions we conclude that the CARE$^{\Sigma M}$ Program isn't sufficiently rigorous to prevent the OTC version of Plan B® from being used by young girls who can't safely use the product without the supervision of a practitioner licensed by law to administer the drug, Plan B® will remain Rx-only for women of all ages."

What, in your opinion, constitutes a "sufficiently rigorous" program? How much evidence would you need to support a decision to deny Plan B's OTC application entirely—considering the overwhelming scientific evidence demonstrating its safety and efficacy, in addition to over 70 from major medical organizations?

Answer 2b. Duramed provided revisions to its CARE$^{\Sigma M}$ program that were considered to be "sufficiently rigorous" by the Agency. Duramed satisfied FDA that it would take steps to monitor the implementation of the program and report to FDA periodically regarding the results of its monitoring program. FDA intends to monitor the program's effectiveness so that we can discuss with the sponsor further modifications if necessary to prevent inappropriate use of Plan B.

Question 3. A consequence of the FDA's refusal to make a decision on Plan B has been a deterioration of trust in the integrity of this Agency. Last year, The New England Journal of Medicine published a damning op-ed titled "A Sad Day for Science at the FDA." And the GAO report made clear that the FDA process and decisionmaking process was highly atypical and suspect. Out of 67 over-the-counter applications made in the past decade, this was the only one that was not approved after the advisory committee recommended approval and the only one in which the action letter was signed by the Director of the Center for Drug Evaluation and Research.

The Journal article labels the Plan B controversy as "a mockery of the process of evaluating scientific evidence,"and concludes with a haunting question, "Will we ever again be able to believe in the FDA's independence?" Given the recent actions of the FDA leadership, I fear I cannot dismiss this question with confidence.

An editorial in the *New York Times* from March 25 of this year said the following of the FDA's nondecision on Plan B:

> "We don't generally approve of holding nominations hostage to other political objectives. But Senators Hillary Clinton and Patty Murray surely have good cause to block a vote on the nomination of Dr. Andrew von Eschenbach to become commissioner of the Food and Drug Administration until the Agency makes a final decision on the morning-after pill. There is no excuse for the administration's endless obfuscation and delays on making the pill available without a prescription when the overwhelming bulk of expert opinion says it is safe to do so."

Dr. von Eschenbach, the bottom line here is that the public health community and much of the general public has begun to question the allegiances of the FDA. For the sake of the Agency's reputation and good standing in the public, which directly impacts its effectiveness. What can the FDA do and what can Members in this chamber do to further expedite this already long-overdue decisionmaking process?

Answer 3. On August 24, 2006, FDA approved the amended sNDA from Barr Laboratories allowing OTC sale of Plan B® to adults 18 and older. Plan B will be available to women 17 and younger by prescription.

Question 4a. We know that the FDA's advisory panel voted overwhelmingly (23 to 4) that this drug should be available over the counter. We know that ACOG, the America Academy of Pediatrics, the American Medical Association and more than 70 other major medical organizations have recommended that the application should be approved. And we know that the New England Journal of Medicine believes what has taken place flies in the face of science.

When I questioned Mr. Crawford in March 2005 regarding Plan B's application, he told this committee and I quote: "I can assure you that this decision will not be based on politics, it will be based on science . . . I don't think it's going to be a long delay."

It's been almost a year and a half since Mr. Crawford made these claims and sadly we can see his promises have not been kept.

What principles do you believe should guide the FDA when it makes decisions about what drugs may be available over the counter?

Answer 4a. The statutory standards established by Congress and the provisions of FDA's regulations guide the FDA when it makes decisions about what drugs may be available over the counter. FDA's regulations provide that FDA will approve a switch to OTC use when it finds that prescription dispensing is "not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and . . . the drug is safe and effective for use in self-medication as directed in proposed labeling."

Such switch applications generally include data from actual use and labeling comprehension studies to demonstrate that the product can be safely and effectively used without the supervision of a practitioner licensed by law to administer the drug. FDA may approve an NDA application only when, among other things, the investigations submitted in the application include adequate tests showing whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling and when there is sufficient information to determine from the application whether the drug is safe for use. FDA will apply these statutory standards to any switch application submitted to it.

Question 4b. Under what circumstances do you believe it is appropriate for the FDA to override such strong scientific evidence in making such decisions? What more information does the FDA need to make a decision on Plan B?

Answer 4b. On August 24, 2006, FDA approved the amended sNDA from Barr Laboratories allowing OTC sale of Plan B® to adults 18 and older. Plan B will be available to patients 17 and younger by prescription.

Question 5. Dr. von Eschenbach, I can't help but notice a gradual increase in the age deemed acceptable for appropriate use of Plan B. Allow me to describe the following timeline of this age discussion:

In July 1999, the U.S. Food and Drug Administration approved Plan B, finding it safe and effective for women of all ages to use as a prescription product. On December 16, 2003, the FDA's independent panel of experts votes 23 to 4 to recommend Plan B be made available OTC, with no age restriction. The panel also voted unanimously that Plan B is safe for nonprescription use.

Despite these findings, on May 6, 2004, Dr. Steven Galson, Acting Director of the Center for Drug Evaluation and Research overrode FDA professional staff rec-

ommendations and issues a "not approvable" letter to Plan B's manufacturer, citing concerns about young teens using the drugs.

Two months later, [July 22, 2004] Barr Pharmaceuticals submitted a revised OTC proposal to FDA, which would make it available to women 16 and older without a prescription while requiring one for women 15 and under. Despite this response to their stated concerns, the FDA failed to make a decision within the deadline imposed under Federal law governing performance standards.

In 2005, Mr. Crawford wrote a letter to a Mr. Joseph Carrado, Senior Director of Regulatory Affairs at Duramed Research, a subsidiary of Barr Pharmaceuticals. Within the text of his letter, Crawford explicitly states that the Center for Drug Evaluation and Research (CDER)'s findings "support the safe use of Plan B as an OTC product, but only for women who are 17 years of age and older."

This year, however, in a letter to Mr. Carrado, written just yesterday, you state that the FDA believes the "appropriate age for OTC access [for Plan B] is 18."

Dr. von Eschenbach, what prompted the addition of a year to the FDA's criteria for what constitutes the "appropriate age" for Plan B? Did new scientific research lead to your move from 17 to 18 years of age? If not, how do you explain your departure from Mr. Crawford's words just a year ago?

Answer 5. The Center for Drug Evaluation and Research (CDER) at FDA determined that the data submitted by the sponsor (Duramed or Barr) in its 2004 application supported OTC use for women 17 and older. In considering the difficulty of enforcing an age-based restriction on the availability of this oral hormonal contraceptive, however, I have concluded that 18 (rather than 17) is the more appropriate cutoff to best promote and protect the public health. The State-regulated pharmacies that will be dispensing Plan B® under Barr's voluntary Convenient Access, Responsible Education (CARE) program (as well as society as a whole) are more familiar with 18 as a cutoff age. I understand that in all 50 States, 18 is the age of majority (i.e., the legal delineation between minor and adult), and retail outlets, including pharmacies, are familiar with using 18 as the age of restriction for the sale of certain products. With regard to the sale of certain drug products, the legal age to purchase FDA-approved non-prescription nicotine replacement therapy products is 18. Moreover, I understand that as a matter of State law, many products routinely sold by pharmacies, e.g., tobacco products and nonprescription cough-cold products like pseudoephedrine are restricted to consumers 18 and older. The approach builds on well-established State and private sector infrastructures to restrict certain products to consumers 18 and older. This approach should, therefore, help ensure safe and effective use of Plan B.

FDA AUTHORITY

Question 6. Several questions have been raised as to whether the FDA has the legislative and regulatory authority it needs to carry out its mission of ensuring the safety of food and drugs used by American consumers. 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 6. FDA is fully capable of carrying out its mission under its current statutory and regulatory authority.

Question 7. 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 7. Throughout my career as a physician, I have believed that only the discipline of scientific inquiry could provide an accurate and reliable understanding of disease and guide the development and application of interventions. This is a belief that I have embraced as an administrator. To embrace scientific research not as an end but as a means to illuminate a path to future progress is the ideology that must guide FDA's decisions regarding the effectiveness and safety of the innovative products that will impact the health and welfare of the public. The leadership of FDA who are responsible for the integrity of the regulatory process must be dedicated to providing the tools of modern science and assuring the application of the rigor and discipline of the scientific method. This leadership team must be comprised of a diverse group of experts in both the science and policy components of the regulatory process. In addition to their professional qualifications, I believe their commitment to collaboration and placing the Agency before personal agendas as well as their devotion to integrity and public service are essential requirements. At present there are no pending candidates for the senior leadership team.

Question 8. Over 1,000 scientists at the FDA recently responded to a survey conducted by the Union of Concerned Scientists, who were seeking information about the ways in which career scientists felt they were able to conduct their work without undue political or commercial interference. Forty percent of the employees who responded noted that their morale was poor or very poor. What steps do you plan to take to restore morale among the career employees at the FDA?

Answer 8. FDA's workforce is comprised of over 12,000 incredibly talented and highly trained professionals who epitomize the true meaning of the word public servant. It is important for everyone to know that if confirmed, their support and guidance will be my greatest asset in leading the FDA.

As the FDA regulates almost 25 percent of all the products Americans consume, its talented and dedicated employees continue to set the Gold Standard that is emulated around the world but never equaled. This standard of achievement must not change. But the world around us is changing and the FDA of today is faced with new challenges and the FDA of tomorrow will encounter incredible opportunities.

I am committed to recruiting and retaining top staff to face these new challenges and to support the Agency's important public health mission.

BIOGENERICS

Question 9. I would like to followup with you on an issue I raised with Gary Buehler, Director of the FDA Office of Generics, at a recent Aging hearing regarding generic biologics.

I recognize that the FDA has been very public about its belief that it does not have the legislative authority to develop a pathway that would allow the vast majority of generic biologics to enter the market. However, the FDA began working on drug-specific guidance documents 7 years ago—during the Clinton administration—to provide information to companies about 2 biologics—insulin and growth hormone—drugs that you have asserted authority over. While these guidance documents are not an explicit pathway, they would certainly facilitate bringing a biogeneric for each of these drugs to the market. But just last month, after 7 years, the FDA announced that it is reversing course and will instead begin all over again and develop industry-wide guidance on this issue.

So now even where the FDA has accepted authority to facilitate bringing a generic to the market, you have spent 7 years and missed the opportunity to save millions of dollars for consumers and taxpayers. In fact, just for insulin and growth hormone, the Medicaid program spent $752 million in 2005 (calculation based on CMS data). If a biogeneric had been on the market in 2005, the Medicaid program could have saved over $100 million on these two drugs alone. And of course the savings to Medicare and the health system overall would be much greater.

Why after 7 years did the FDA decide to change course? What happened to the insulin and growth hormone specific documents you were working on, and will you release documentation of their development to the HELP Committee? In light of the significant opportunity for cost-savings, will you release these two guidance documents? What action will you take to provide industry-wide guidance and how will you make it specific enough to be helpful to companies considering biogeneric development for drugs as different as insulin and growth hormone?

Answer 9. Protein products may be approved as drugs by FDA under section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act or licensed as biological products under section 351 of the Public Health Service (PHS) Act. For products approved under section 505 of the FD&C Act, we believe there is existing authority to allow applications for follow-on protein products to be approved under sections 505(b)(2) or 505(j) of the FD&C Act where scientifically appropriate. There is no abbreviated approval pathway for protein products licensed under 351 of the PHS Act analogous to sections 505(b)(2) or 505(j) of the FD&C Act for drugs.

Please be assured FDA's consideration of regulatory issues related to follow-on protein products is progressing. FDA held two public meetings (September 2004 and February 2005) and co-sponsored a workshop (December 2005) on scientific issues related to follow-on protein products. These meetings resulted in a large number of comments and concerns from the interested parties that are being considered as we develop policies for regulating these products, including forms of insulin and human growth hormone.

The Agency has reconsidered issuing, at this time, the draft guidance documents on human growth hormone and insulin that you referenced for a number of reasons. After re-assessing these "product-specific" draft documents, FDA has determined that it would be more appropriate to initially publish guidances that are more broadly applicable to follow-on protein products in general. FDA expects that this approach will provide useful guidance to the industry, while ensuring that we do

not stifle innovation and the utilization of state-of-the-art technologies. In addition, a sponsor may contact the Agency to request advice on a case-specific basis regarding the development of a follow-on protein product for submission in an application under section 505 of the FD&C Act.

With regard to your request for the Agency to release its preliminary draft guidance documents on human growth hormone and insulin, I note that these internal draft documents were never finalized and were not cleared by Center for Drug Evaluation and Research (CDER) management, thus they do not necessarily reflect CDER's current thinking on these topics. For this reason, we would not disseminate these deliberative documents outside FDA.

I do want you to know, however, that even as guidance documents on follow-on protein products are being developed, the Agency has been moving forward with the review and approval of those follow-on protein products regulated as drugs for which the sponsors have met the statutory and regulatory approval requirements under section 505. Most recently, we have approved Fortical (calcitonin salmon recombinant) Nasal Spray in August 2005, Hylenex (hyaluronidase recombinant human) in December 2005, and Omnitrope (somatropin [rDNA origin]) in May 2006.

Question 10. Since 2004, the FDA has been studying the issue of follow-on protein products, which refers to proteins and peptides that are intended to be sufficiently similar to already approved products—essentially, generic versions of biologic protein products that may already be on the market. Although the FDA was supposed to release a White Paper to provide further guidance on this topic in 2005, nothing has yet been released. When will you release this guidance?

Answer 10. The Agency has been studying the issue of follow-on protein products because of the important public health objectives that are advanced by an approval system for such products. Applications that rely on existing scientific knowledge, subject to the protection of intellectual property rights, can avoid unnecessary duplication of research and lead to decreased costs to consumers, industry, and FDA. Further, such reliance on existing knowledge obviates certain ethical concerns related to medically or scientifically unjustified preclinical and clinical testing.

We generally use the term follow-on protein products rather than generic biologics to refer to protein and peptide products that are intended to be sufficiently similar to a product already approved or licensed to permit the applicant to rely for approval on certain existing scientific knowledge about the safety and effectiveness of the approved protein product. Your question refers to "generic versions of protein products." FDA generally uses the term "generic" to refer to drugs approved under section 505(j) of the FD&C Act, which are therapeutically equivalent to, and therefore substitutable for, the innovator product. Although the generic drug approval pathway set forth in section 505(j) of the FD&C Act may be used to approve follow-on protein products where the State of the science is adequate to demonstrate "sameness" of the active ingredient, and for which clinical safety and effectiveness studies are not necessary, most follow-on protein products are expected to be reviewed in section 505(b)(2) applications.

Numerous protein products, however, are licensed as biological products under section 351 of the Public Health Service (PHS) Act, and are not approved as drugs under the FD&C Act. There is no abbreviated approval pathway for protein products licensed under section 351 of the PHS Act analogous to sections 505(b)(2) or 505(j) of the FD&C Act for drugs.

Please be assured that FDA's consideration of regulatory requirements for follow-on protein products is progressing. FDA has sought input from stakeholders and conducted an extensive public discussion on scientific issues relating to the development and approval of follow-on protein products, including two public meetings (September 2004 and February 2005) and a co-sponsored workshop (December 2005). The public meetings resulted in a large number of comments and concerns from interested parties that are being considered further as we develop policies for regulating follow-on protein products. FDA recognizes that guidance for industry would be helpful, and intends to publish guidance broadly applicable to follow-on protein products in a timely manner. FDA expects that this approach will provide useful guidance to the industry, while ensuring that we do not stifle innovation and the utilization of state-of-the-art technologies. In addition, a sponsor may contact the Agency to request advice on a case-specific basis regarding the development of a follow-on protein product for submission in an application under section 505 of the FD&C Act.

I do want you to know, however, that even as guidance documents on follow-on protein products are being developed, the Agency has been moving forward with the review and approval of those follow-on protein products for which the sponsors have met the statutory and regulatory approval requirements under section 505. Most re-

cently, we have approved Fortical (calcitonin salmon recombinant) Nasal Spray in August 2005, Hylenex (hyaluronidase recombinant human) in December 2005, and Omnitrope (somatropin [rDNA origin]) in May 2006.

Question 11. We know that a number of brand biopharmaceuticals are now eligible to have generic competition or will be eligible over the next few years. Yet, there seems to be very little movement by FDA to bring affordable generic biologics to the market in the United States. Without FDA action, naming organizations in both the United States and Europe are delaying action on regulations which will guide the marketing of these types of biogenerics. As a result, consumers worldwide are denied access to generics that are proven safe, but cost less.

At the upcoming World Health Organization meeting of global regulatory agencies, will the FDA help to resolve questions around the naming of biogenerics to ensure that Americans and patients around the world will soon have access to affordable medicine?

Answer 11. FDA has been moving forward with the review and approval of those follow-on protein products for which the sponsors have met the statutory and regulatory approval requirements under section 505 of the FD&C Act. Most recently, we approved Fortical (calcitonin salmon recombinant) Nasal Spray in August 2005, Hylenex (hyaluronidase recombinant human) in December 2005, and Omnitrope (somatropin [rDNA origin]) in May 2006.

We have considered issues related to the established (nonproprietary) name of follow-on protein products on a case-specific basis, informed by our public meetings on scientific considerations related to follow-on protein products in September 2004 and February 2005. The Agency is not aware of any delay in marketing a follow-on protein product attributable to a question regarding the appropriate established name for the product, which typically is resolved during the review process and prior to product approval. It should be noted, however, that a common established name does not necessarily indicate therapeutic equivalence (and therefore substitutability or interchangeability) of two drug products absent an "A" therapeutic equivalence rating in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book").

FDA looks forward to participating in the upcoming World Health Organization meeting of global regulatory agencies and discussing its issues related to the international nonproprietary name selection process for "biosimilar" or follow-on protein products.

FLU VACCINE

Question 12. 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.

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 12. While there are significant elements of risk in the industry that are beyond FDA's control, in particular underlying market forces and the inherent uncertainties and complexities of flu vaccine production, the Agency has made significant changes in certain areas in an effort to help prevent future problems. Since 2004, FDA has conduced 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. The Agency also interacts extensively with licensed manufacturers to address issues that may arise during annual production. FDA has also reached out to manufacturers to share important technical information and to encourage preventive approaches that specifically address quality in vaccine manufacturing.

FDA is also working to facilitate increased diversification and capacity in flu vaccine manufacturing. FDA has contacted major manufacturers of influenza vaccine throughout the world to stimulate interest in producing vaccine for the U.S. market. In March 2006, FDA released the guidance document, "Draft Guidance for Industry, Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines." For new vaccine developers, the document recommends clear pathways for both traditional and accelerated approval approaches. Accelerated approval al-

lows for evaluation based on biological indicators (e.g., the immune response to the vaccine) likely to demonstrate effectiveness. This outreach to manufacturers and the availability of accelerated approval has resulted in one additional vaccine product approval for the 2005–2006 season, and the possibility for others in future flu seasons.

A major factor contributing to current risks in flu vaccine manufacturing is the inherent nature of current, egg-based technologies. FDA is therefore undertaking efforts to facilitate development of influenza vaccines using new technologies, including cell based, and other novel types such as DNA and synthetic peptide, and is working closely with HHS, NIH and product developers to help advance and evaluate such promising new technologies.

PEDIATRIC RULE

Question 13. I believe that it's extremely important to ensure that the drugs we give to our children have been proven to be safe for use in children, which is why I worked with Senator DeWine and my other colleagues in the Senate to pass the Pediatric Research Equity Act to codify the pediatric rule—the FDA guideline that required such testing, and which was promulgated during the Clinton administration.

The Pediatric Research Equity Act, in conjunction with the Best Pharmaceuticals for Children Act (BPCA), which provides pediatric exclusivity incentives to manufacturers that conduct pediatric studies, have worked to improve confidence in the safety of the drugs that we provide to children.

The FDA allows companies to request waivers from requirements to conduct pediatric studies for drugs that are not likely to be used in the overall pediatric population, such as drugs for ovarian cancer. Some companies that should be seeking waivers are instead conducting pediatric studies to receive the 6 months of exclusivity made available under the BPCA. Such abuse of the system undermines support for this important incentive and needs to be addressed.

What actions should the FDA take to ensure that drugs that are obviously not geared for pediatric populations do not qualify for the exclusivity incentives under the BPCA?

Answer 13. I can assure you that FDA carefully considers the potential for public health benefit of a given drug in pediatric patients before issuing a Written Request to a sponsor for pediatric studies under BPCA. FDA would not issue a Written Request for studies in children when there is evidence that strongly suggests the drug would be ineffective or unsafe in pediatric patients; when the studies would be ethically controversial (unless the potential public health need is so great that studies are warranted); or when there is insufficient safety information for studies to be conducted. Written Requests are typically reviewed by a multidisciplinary committee prior to being issued; this review further ensures that Written Requests are appropriately issued.

There are several reasons why a Written Request might be issued under BPCA even though studies were waived or deferred under PREA. BPCA, like PREA, allows FDA to request pediatric studies for any and/or all approved adult indications that apply to the pediatric age group. However, in contrast to PREA, BPCA also allows FDA to request pediatric studies for indications that are not approved in the adult population. For example, a product that is used to treat hypertension in adults may, by its mechanism of action, also be useful to treat pulmonary hypertension in newborns. Under PREA, there is no way to obtain those studies in newborns because PREA is limited to indications for which the sponsor has obtained or is seeking approval in adults. Under BPCA, we could issue a Written Request to the sponsor asking that they submit studies for pulmonary hypertension in newborns. We could issue the Written Request at any time and not have to wait until a sponsor informs us they want to study the product in the adult population.

Products for orphan indications (those indications occurring in fewer than 200,000 patients) may be studied under BPCA, but are exempt from the requirements of PREA. This provision was included in BPCA to ensure that treatments for rare diseases are studied in the pediatric population. In some cases, a drug with an approved indication that does not occur in the pediatric population may be used off-label in pediatric patients to treat rare childhood diseases such as McCune-Albright Syndrome or osteogenesis imperfecta. When possible in these cases, we want to have information that can be included in the label and studies under BPCA are often the only way to get this information.

Question 14. There has been much controversy over the use of antidepressant medications in pediatric populations 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 14. The use of psychotropic medications in children and adolescents is an issue of major concern to FDA. BPCA, in particular, has contributed to the development of important information. Over the past few years, we have taken a number of actions related to the use of selective serotonin reuptake inhibitors (SSRIs) and other anti-depressants in children and adolescents. These actions were based largely on FDA's review of clinical trials conducted in children under the pediatric exclusivity incentives. Review of these study data contributed toward FDA's conclusion that antidepressants are associated with an increased risk of suicidal thinking and actions in adolescents with certain psychiatric disorders. This conclusion led to issuance of public health advisories, revised labeling for all SSRIs and other antidepressants, and patient medication guides. The FDA Psychopharmacologic Drugs and Pediatric Advisory Committees reviewed these actions and considered them appropriate. BPCA has stimulated studies of other psychotropic drugs as well and has identified that many of these products that work for depression in adults do not appear to have the same magnitude of effect in children. Without these studies it is doubtful we would ever have been able to develop the level of information that we did regarding how children react differently than other patient populations.

GENERIC DRUGS

Question 15. There has been a well-publicized backlog of generic drug approvals at the FDA. What action will you take to clear this backlog? What additional authority or resources do you need to reduce the amount of time it takes to bring safe, generic pharmaceuticals to market?

Answer 15. We share your interest in speeding the availability of generic drugs. FDA has taken a number of significant steps to provide greater access to affordable prescription medications, including unprecedented steps to lower drug costs by helping to speed the development and approval of low-cost generic drugs after legitimate patents have expired on branded drugs. Generic drugs typically cost 50 to 70 percent less than their brand-name counterparts. In 2003, FDA published a final rule to improve access to generic drugs and lower prescription drug costs for millions of Americans. The rule limits an innovator drug company to only one 30-month stay of a generic drug applicant's entry into the market for resolution of a patent challenge. These changes will save Americans over $35 billion in drug costs over the next 10 years, and will also provide billions in savings for the Medicare and Medicaid programs. We were pleased that elements of this rule were codified as part of the Medicare law and that, with FDA's technical assistance, the law added additional mechanisms to enhance generic competition in the marketplace.

In addition, since fiscal year 2001, the Administration and Congress have increased funding for FDA's generic drug program by 66 percent, a clear sign of the important role played by OGD. These increases have enabled FDA to hire additional expert staff to review generic drug applications more quickly and initiate targeted research to expand the range of generic drugs available to consumers. While there remains work to be done, as I will discuss, we have been able to produce significant reductions in approval times for generic drugs since 2002 that consequently will save consumers billions by generally reducing the time for developing generic drugs and making them available.

In addition, our Office of Generic Drugs (OGD) has worked tirelessly to find efficiencies in the generic drug application review process. OGD is incorporating several changes in the process to reduce review time, including:

- Reviewing Drug Master Files (DMFs) prior to the time the related ANDAs are assigned since the DMF evaluation is often the limiting factor in completing the ANDA review.
- Utilizing telephone conversations with ANDA sponsors, when appropriate, to resolve deficiencies more efficiently and expeditiously.
- Assigning applications to reviewers with related expertise or experience with a particular drug class.
- Utilizing a new format for the chemistry review called question based review. It is based on the structure of the International Conference on Harmonization Common Technical Document for the chemistry review.
- Utilizing a team review approach for "clusters" of applications for the same product.

OGD continues to seek ways to make the review processes and interactions with industry more efficient, including seeking better information technology solutions.

DRUG SAFETY

Question 16. In April, you engaged a consulting firm to evaluate post-marketing study commitment process. The report from that firm is not expected for another year. In the meantime, what action will you be taking to ensure that companies engage in post-marketing studies?

Answer 16. As noted in your question, FDA is in the process of undertaking a review of the decisionmaking process behind requests for Post-marketing Study Commitments (PMCs) for human drugs, including biological drugs. An outside contractor has been hired to evaluate how different review divisions decide to request PMCs, decisions surrounding what kinds of PMCs to request, and what are reasonable timeframes for completing PMCs. The study will serve to assist FDA in determining if better guidance is needed for industry and to ensure there is standardization of the procedures. While this study is being conducted, the Centers within FDA have undertaken activities in the meantime to improve the response on post-marketing and post-approval studies for human drugs (including biological drugs).

Post-marketing study commitments (PMCs) for approved drug products are studies that a sponsor either is required or agrees to conduct after FDA has approved a product for marketing to further define the safety, efficacy, or optimal use of a product. In some cases, the studies can take years to complete, even if everything is going according to schedule. In other cases, there are considerable obstacles (e.g., difficulty in recruiting patients and investigators to participate in a clinical trial when an approved therapy is available) that must be addressed before the studies can be completed. In these cases, FDA works closely with sponsors to address these obstacles. It should also be noted that approximately 38 percent of the currently pending PMCs for new drug applications were established in applications approved between October 1, 2003, and September 30, 2005, and thus, depending on the complexity of the study, FDA would expect that many of these studies would not have been initiated yet.

FDA takes its statutory obligations under the Food and Drug Administration Modernization Act of 1997 (FDAMA) to track and monitor the progress of PMCs very seriously. FDA recently published a final guidance to industry to describe in greater detail the content, format, and timing of PMC annual status reports submitted by the drug industry. Furthermore, FDA reports annually in the Federal Register on the performance of applicants in conducting their PMCs and maintains a public Website that contains the information that FDA is required under FDAMA to make available to the public. These initiatives, along with other FDA internal procedures, are all intended to ensure that industry undertakes their commitments and completes them in a timely manner.

Question 17. For months, Tysabri, a drug used to treat multiple sclerosis, was unavailable to patients, after several patients in clinical trials developed a serious brain infection that proved fatal in two cases. It is estimated that 1 in 1000 patients who take Tysabri will experience such complications.

Although Tysabri was returned to the market earlier this year under a special distribution program, many MS patients, including several of my constituents, who had experienced treatment gains with Tysabri were concerned at the sudden withdrawal of this drug. Some argued that they understood the treatment risks, and would like to have had the option to continue taking a drug which helped them halt progression of an ultimately fatal disease.

As new therapies for debilitating chronic diseases like MS emerge on the market, how will you work with patient groups to balance concerns over safety with the desire to get a clinically effective but potential risky drug to a population that will benefit from it?

Answer 17. Under the Federal Food, Drug, and Cosmetic (FDC) Act and related statutes, the Government has a vitally important role in helping to ensure that the medical products upon which patients and their health care practitioners rely are both safe and effective. These safeguards are particularly important for our most vulnerable citizens, those who are desperately ill. We believe the existing programs under which patients can obtain access to experimental therapies, and those under which we expedite approval of such therapies, establish the appropriate framework for achieving our mutual goal of providing patients with serious and life-threatening diseases the earliest reasonable access to promising therapies. These programs were codified in the "Food and Drug Administration Modernization Act of 1997."

Of course, we recognize the value of even more effective access programs, and we are open to improving the effectiveness of these processes. FDA's Office of Special

Health Issues works with patients and their advocates to encourage and support their active participation in the formulation of FDA's regulatory policy. The staff is familiar with the concerns confronting patients and families dealing with life-threatening and debilitating illnesses.

CDER routinely consults with the American people in making its decisions about the drugs that they use. It holds public meetings to incorporate expert and consumer input into its decisions. The center also announces many of its decisions in advance so that members of the public, academia, industry, trade associations, consumer groups, and professional societies can comment and make suggestions before decisions become final. In addition, CDER holds annual public meetings with consumer and patient groups, professional societies, and pharmaceutical trade associations to obtain enhanced public input into its planning and priority-setting practices. The Agency's public health mission remains constant: to ensure that the benefits of drug products made available to the public outweigh known risks.

PREGNANT WOMEN—PREGNANCY REGISTRIES

Question 18. The FDA Website contains information about pregnancy registries—surveillance studies to help determine the safety of drugs in utero. These types of studies are extremely important so that we can develop guidelines that help us not only prevent adverse health impacts in the womb, but also to help women with health concerns, such as cancer, depression, or other chronic diseases, maintain good health during and after their pregnancies. However, your Website has not updated information on these types of registries since July 2004. How will you improve the ability of the Agency to make women aware of these studies and their results? How will you work with manufacturers to encourage them to engage in these types of studies and disseminate their results?

Answer 18. Our Office of Women's Health will be updating the pregnancy registries Website within the next 12 months. FDA issued an industry guidance document, "Establishing Pregnancy Exposure Registries," in August 2002. When a pregnancy registry is implemented, FDA works with the sponsor of the registry to ensure that healthcare providers and patients who may be eligible for participation are aware of it. This may be done through a variety of measures, including publication of the registry contact information in labeling, patient package inserts, notification of teratogen information services in States, and even use of the product's detail sales force. Additionally, in April 2005, FDA finalized guidance to staff, entitled "Evaluating the Risks of Drug Exposure in Human Pregnancies," to assist them in evaluating human fetal outcome data generated after medical product exposures during pregnancy.

Unfortunately, the current system of having a separate registry for every drug for which a pregnancy registry is implemented is highly inefficient and makes communication regarding, and even participation in, registries cumbersome at every level. FDA continues to work with other agencies, especially the CDC, to find ways to build a more consistent, robust system of capturing data on the safety of drugs used in pregnancy.

iPLEDGE PROGRAM

Question 19. Isotretinoin, also known as Accutane, is a drug used to treat severe acne, has been found to cause miscarriages and birth defects. According to a study by Roche, nearly 2,000 women have become pregnant while on the drug since it was approved over 20 years ago. Three hundred and eighty-three gave birth, with half of those children being born with birth defects.

In order to prevent pregnancy from occurring while on this drug, the FDA established the iPledge program in March of this year. This Internet-based program tracks compliance with prescription requirements, which include mandates to ensure female patients use two forms of birth control and take monthly pregnancy tests. All patients must also undergo tests to monitor other conditions, including cholesterol and liver function. These important safety protections help to ensure that health will not be endangered.

However, the administrative requirements of the iPledge program have made it more difficult for patients to access this drug, and physicians report long wait times in seeking assistance from iPledge personnel. What actions will you take to reform the iPledge program so as to protect women's health while reducing the administrative burden for both patients and physicians? Will you be releasing data on the number of pregnancies that may occur with this system, so that we can judge its effectiveness?

Answer 19. FDA has worked closely with isotretinoin sponsors and their vendor, Covance Inc., to maintain a critical balance between access to the drug by patients

who need it and ensuring its safe use. In response to concerns raised by dermatologists and pharmacists in recent weeks, FDA has ensured that rapid and significant progress has been made by the sponsors and Covance to address operational aspects of the program. The specific measures taken include an increase in iPLEDGE call center staffing to handle the expected increases in call volume and user questions, as well as an enhanced system to process requests for new passwords by users who have forgotten or lost their original passwords.

MINORITY HEALTH

Question 20. In 2005, the FDA approved BiDil, the first race-specific drug. BiDil is a combination of two drugs—75 milligrams of hydralazine and 40 milligrams of isosorbide dinitrate—used to treat high blood pressure and chest pain. Non-race specific generic versions of these two drugs are available. Since BiDil was approved, significant concerns have been raised about the ethics of developing and marketing race-specific drugs. What will you do to address these concerns when other race-specific drugs are submitted for approval? How will you work with patient populations to ensure that such concerns are heard by your agency, especially since there is no currently existing Office of Minority Health at the FDA?

Answer 20. The growing interest in targeted therapy could lead to cases in which an effect is shown for a narrow group, but there is very little information about the rest of the population. Thus, when a therapy is shown to be effective for a responsive subgroup, the following critical questions to be considered include: (1) how much data should be expected on the drug's effects in other groups, (2) how small an effect needs to be detected or excluded in those groups, (3) when should the data on those other groups be expected (before or after approval, and how long after), and (4) to what extent can FDA require further studies. It is important to note, however, that it is appropriate to approve a product for a specific race or demographic group when the legal standard for approval is met, given adequate attention to the points above.

FOOD SAFETY—MERCURY IN FISH

Question 21. In 2004, the FDA and the EPA released the Joint Federal Advisory for Mercury in Fish, which provided information on levels of mercury in fish to help guide the diet choices for pregnant women, parents, and others. Recent data has uncovered higher than expected levels of mercury in both imported tuna, which makes up about half the American tuna market, and other types of fish, such as mahi mahi, that were thought to be low in mercury. Yet despite this new data, the FDA has not updated its advisory. How will you ensure that such updated information is made available to consumers on a more timely basis?

Answer 21. In March 2004 FDA and EPA issued a joint advisory to help women who may become pregnant, pregnant women, nursing mothers, and parents of young children get the health benefits of eating fish and shellfish while reducing prenatal and early childhood exposure to mercury. The advisory, based on data collected from various brands of tuna and other species of fish from both domestic and international sources, provides specific recommendations about portion sizes of fish with low and moderate mercury levels, and recommends against consumption of specific fish species with higher levels of mercury. These recommendations remain valid. We continue to collect and analyze data on mercury levels in fish.

The consumer advisory is being aggressively disseminated. For example, FDA and EPA are jointly sponsoring a public education campaign to reach women planning on becoming pregnant, pregnant women, nursing mothers, and parents of young children about the methylmercury advisory. FDA's outreach includes over 9,000 media outlets, including those that specialize in reaching women. In addition, information about the advisory has been sent to over 50 health-care provider organizations.

An ongoing national survey conducted by the Centers for Disease Control and Prevention shows that about 94 percent of U.S. women of childbearing age have less methylmercury in their bodies than the EPA Reference Dose, a level of exposure established with a substantial margin of safety to protect the fetus from neurological harm. The remaining approximately 6 percent of women in the target population are, for the most part, only slightly over the Reference Dose, and still retain most of the substantial margin of safety that is built into it. Because a Reference Dose is not intended to separate safe levels from unsafe levels, we would not anticipate the risk for those who are exposed slightly over the Reference Dose to be significantly different than it is for those who are exposed at or below the Reference Dose.

Question 22. In a letter I sent to you in February of this year, I urged you to take the following steps to address concerns around levels in mercury in fish, especially questions about the methodology used by the FDA to take mercury samples:

• Expand the testing system and increase sampling sizes for commonly consumed fish. We need a better baseline to ensure that we can better detect high levels when they do occur.

• Perform further investigations into samples that do register high levels of mercury. From the data available on the FDA's Website, there is no way to determine what factors might contribute to the increase in mercury levels found in 6 percent of the samples of light tuna—such as possible inclusion of yellowfin tuna in the sample.

• Provide clear, detailed summaries of the results of your monitoring program on your Website, in addition to providing the actual data available at *http://www.cfsan.fda.gov/~frf/seamehg2.html.*

What action have you taken to implement these steps at the FDA?

Answer 22. Thank you for your suggestions. FDA will continue to provide summaries of the results of our monitoring program on our Website (*http://www.cfsan.fda.gov/~frf/seamehg.html*). We have not implemented your other recommendations relating to our sampling program because, as explained in FDA's April 13 response to your letter, our findings of methylmercury concentrations in commercial fish are either within the variations in methylmercury that we know to exist or are not so high as to represent a significant public health issue. In response to your suggestion of expanding the monitoring program, FDA remains convinced that the number of samples collected for methylmercury analysis provides us with sufficient data to make appropriate risk management decisions and represents an appropriate allocation of our public health resources. As it is currently designed, the monitoring program allows us to track mercury levels in those fish species that tend to have the higher levels and are the most frequently consumed.

It is important to recognize that fish consumption is typically so low in this country that exposure to methylmercury, as revealed by national survey data from the Centers for Disease Control and Prevention, remains low for most people regardless of the variations in the methylmercury concentrations of the fish they eat. Actual exposure to methylmercury, i.e., the amount of methylmercury that people have in their bodies, is a key public health indicator relative to the concentration of methylmercury that might be in any given fish.

We know of no confirmed cases of adverse effect from methylmercury from eating commercial fish in the United States. However, it is essential that we develop a better understanding of the likelihood of adverse effects at the relatively low levels of exposure generally experienced by U.S. consumers. For that reason, we are in the process of upgrading our understanding of risk within the U.S. population. This effort involves examining the likelihood of adverse effects through the range of exposures being experienced by U.S. consumers. We look forward to sharing the results with you as soon as they are available.

COLLABORATION BETWEEN THE FDA/CPSC

Question 23. The FDA and the Consumer Product Safety Commission (CPSC) have collaborated on several occasions to address safety risks from food and packaging. Yet while there has been cooperation on specific issues, such as the threat posed by conjac gel candies, there is no standard mechanism to spur greater cooperation. The lack of cooperation leads to jurisdictional issues around items like jumbo mint balls, which caused choking deaths in New York. How will you formalize the relationship between your agency and the CPSC in order to set up a permanent mechanism through which to improve the ability to regulate both foods and their packaging?

Answer 23. FDA has had a close relationship with the Consumer Products Safety Commission (CPSC) since its creation in 1973. This is especially true since some FDA functions and personnel were transferred to CPSC upon its creation. In 1976, FDA and CPSC signed a Memorandum of Understanding (MOU) delineating the areas of jurisdiction of the respective agencies including those involving food and food contact materials. Both agencies continue to operate under that MOU and to closely cooperate in matters where jurisdictional questions may occur. In fact, representatives from FDA's foods program have met with representatives of CPSC as recently as August 14, 2006, to discuss closer cooperation on matters involving food and food contact material. FDA expects to continue these discussions as necessary and to take whatever other steps are appropriate to maintain and improve our ability to work with CPSC to accomplish our respective consumer protection missions.

In the coming months, FDA and CPSC will examine the existing MOU on jurisdiction and work to revise it as needed.

LEAD IN CANDY

Question 24. In December 2005, the FDA released a draft guidance entitled "Lead in Candy Likely To Be Consumed Frequently by Small Children: Recommended Maximum Level and Enforcement Policy." While this guidance recommends that levels of lead in candy not exceed 0.1 parts per million, it also states that "FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities." Why hasn't the FDA taken stronger action against candy that contains higher levels of lead? If the FDA does not have such enforcement authority, what additional authority do you need in order to ensure that no lead exists in candy sold to American children?

Answer 24. FDA is giving a high priority to its monitoring and enforcement activities aimed at keeping candy products with potentially harmful levels of lead from reaching U.S. consumers. Under the Federal Food, Drug and Cosmetic Act, FDA can take action against any food, including candy, which is contaminated with lead at levels that may render the food injurious to health. FDA monitors candy for lead at points of entry into the United States and in domestic commerce. FDA will take enforcement action whenever it encounters a candy product that contains potentially hazardous lead levels.

Enforcement actions available to FDA include seizure for foods in domestic commerce and refusal of entry for foods offered for import into the United States Also, future entries of an imported candy product found to be contaminated would be detained without physical examination until the contamination problem was corrected. FDA can also pursue voluntary recall for food that has been distributed domestically. FDA has, in the past, refused entry into the United States for imported candy products that have been found to contain elevated lead levels.

To further reduce the exposure of children to lead from candy products, FDA plans to issue a guidance, which has been released in draft for comment. When it is issued, the final guidance on lead in candy will provide guidance on the maximum lead level we would expect in candy produced under good manufacturing practices. The guidance will list specific actions candy makers can take to ensure that their products do not exceed the recommended maximum level.

Question 25. In New York City, local legislators passed a law banning candy containing lead, because of the lack of regulation on this issue at the Federal level. How do you plan to improve the responsiveness of the FDA to food safety issues so that national safety standards are as strong as those at the local level?

Answer 25. FDA is able to and does take prompt action in response to food safety concerns under its regulatory authority, including the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, and the Bioterrorism Act of 2002. For example, FDA can take action against any food that contains lead, or other added contaminants, at levels that may render the food injurious to health. Enforcement actions available to FDA include seizure of foods in interstate commerce and refusal of entry for foods offered for import into the United States. Future entries of an imported food product previously found to be contaminated would be detained without physical examination until the contamination problem was corrected. FDA can also pursue voluntary recall for food that has been distributed domestically.

FDA plays a leadership role in food safety through cooperative efforts with our State partners. For example, the Conference for Food Protection is a cooperative FDA-State program, pursuant to which FDA issues nonbinding guidelines that States can adopt under State law and regulatory processes. FDA has similar cooperative provisions for milk and shellfish. In addition, FDA often develops guidance for the regulated community on food safety matters. While these guidance documents are not binding on the regulated community, the regulated community may use them as informal standards, even when they are in the draft, rather than final, stage.

In terms of setting enforceable national standards, FDA frequently issues regulations to address food safety issues. The speed with which such actions can become final and enforceable regulatory requirements is influenced by staff and resource limitations and competing public health priorities, and by our need and desire to fully comply with controlling procedural and policy requirements, including the Administrative Procedures Act, Executive Order 12866, the Small Business Reform Act, the Unfunded Mandates Act, the Paperwork Reduction Act, and other requirements.

With respect specifically to lead in candy, please see our response to your previous question (#24) for information regarding FDA's actions.

Question 26. The FDA is currently considering approving the pre-market applications (PMAs) of Mentor and Inamed Corporations for their silicone breast implants (SBI). However, the FDA is also conducting a criminal investigation of Mentor, including allegations that Mentor provided inaccurate data to hide design problems and higher rupture rates. Has the FDA completed its investigation? If not, will the FDA conclude its investigation before issuing a final decision on the PMAs?

Answer 26. FDA has completed its investigation of Mentor and the case was closed in June. If information arises in the future that causes FDA to question the validity of data in an application, the Agency would not consider approving a PMA without considering how the information may affect our ability to assess safety and effectiveness. In addition, as part of the PMA review process, FDA performs Bioresearch Monitoring (BIMO) and Manufacturing inspections. The BIMO inspection of the sponsor and some investigational sites includes, for example, the review of records to assure the integrity of the data submitted. Any decision we make on the PMA will be made on the basis of a complete evaluation of the safety and effectiveness of the silicone breast implants.

ADDITIONAL QUESTIONS OF SENATOR CLINTON FOR ANDREW C. VON ESCHENBACH

Question 1. The FDA regulates the promotion of prescription drugs, including the content of DTC advertisements. A 2002 GAO report highlighted a change in HHS procedure for reviewing draft regulatory letters that resulted in the issuance of regulatory letters after the misleading advertising campaign was completed. What has the FDA done to correct this problem and ensure that regulatory letters are issued timely?

Question 2. What actions has FDA taken to prevent pharmaceutical companies who have received regulator letters from disseminating new misleading advertising for the same drug?

Question 3. What are FDA's personnel and budgetary commitments for the oversight and regulation of the promotion of prescription drugs, including DTC?

Question 4. Does the FDA review prescription drug advertising on the Internet? What differences have you found with regulation of advertising in that medium compared to broadcast or print?

[Editors Note: The responses to additional questions from Senator Clinton were not available at time of print.]

[Whereupon, at 12:20 p.m., the hearing was adjourned.]

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