

**AGRICULTURE, RURAL DEVELOPMENT, AND
RELATED AGENCIES APPROPRIATIONS FOR
FISCAL YEAR 2007**

TUESDAY, MARCH 14, 2006

U.S. SENATE,
SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 10:05 a.m., in room SD-192, Dirksen Senate Office Building, Hon. Robert F. Bennett (chairman) presiding.

Present: Senators Bennett, Craig, Kohl, and Harkin.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

STATEMENT OF HON. ANDREW C. VON ESCHENBACH, ACTING COMMISSIONER

ACCOMPANIED BY:

KATHLEEN HEUER, CHIEF FINANCIAL OFFICER AND ASSOCIATE COMMISSIONER FOR MANAGEMENT

RICHARD TURMAN, DEPUTY ASSISTANT SECRETARY FOR BUDGET, TECHNOLOGY, AND FINANCE, DEPARTMENT OF HEALTH AND HUMAN SERVICES

STEVE SUNDLOF, DIRECTOR, CENTER FOR VETERINARY MEDICINE

OPENING STATEMENT OF SENATOR ROBERT F. BENNETT

Senator BENNETT. The subcommittee will come to order.

And this morning, we are happy to welcome Dr. Andrew von Eschenbach, who is the acting Commissioner of the Food and Drug Administration. And we also welcome Ms. Heuer and Mr. Turman. We appreciate very much your being here.

This is the second subcommittee hearing we have convened since receiving the President's fiscal 2007 budget request, and it is the first time that Dr. von Eschenbach has appeared before the subcommittee.

The FDA did pretty well under the President's budget process. The budget request, not including user fees and fiscal 2006 supplemental funding, represents an overall increase of \$70 million from the level of funding in fiscal 2006. Not all portions of this subcommittee's budget did as well in terms of the President's recommendations.

The FDA budget includes increases for pandemic influenza preparedness, food defense, drug safety, tissue safety, animal drug and medical device review, and a new initiative, called the Critical Path Initiative, to speed development of medical products.

But it does include more than \$50 million in base funding reductions. We have been given very little information about the impact of these reductions, and I expect that we will discuss those in some greater detail in the hearing this morning.

Now given the fact that we are competing with other subcommittees, had to fight your way down the hall to get around the corner to come in here, and we are in the midst of the budget discussions on the floor, we are going to keep members to 5-minute rounds.

We will use the "early bird" rule. That is, Senators will be recognized in the order of their arrival, and members will be allowed to submit questions for the record. We want all of the questions to the subcommittee to be here by the close of business on the 24th of March.

Senator Kohl and I will be the only two to give opening statements. And when we have finished with our opening statements, then we will go directly to Dr. von Eschenbach for his presentation and then begin the questioning rounds.

So with that statement of the ground rules, Senator Kohl.

Senator KOHL. I thank you, Mr. Chairman.

Dr. von Eschenbach, it is good to see here you here today, and we also want to welcome Ms. Heuer and Mr. Turman as well as the rest of your staffs.

There has been, as you know, lots of interest in your budget, which appears to receive the most robust increase in the entire agricultural appropriations bill. I am pleased to see additional funding for drug and tissue safety as well as avian flu and food defense.

Also in the budget, though, there is a redirection of \$52 million and funding for some important activities and staffing levels actually decreases. These decreased activities, according to your budget, include generic drug contracts, analysis of food import samples, compliance and recall functions, certain safety activities in the biologics program, dietary supplement activities, and inspections of veterinary food and human drugs manufacturers.

This is not at all a complete list. This is obviously a concern, and we are interested to know how the priorities in this budget were determined.

We are hopeful that you will provide detailed information on this redeployment as well as your budgeted increases here today. And so, we look forward to your statement and the opportunity to ask questions.

Thank you, Mr. Chairman.

Senator BENNETT. Thank you.

Dr. von Eschenbach, your prepared statement has been received and will be included in the record at this point in its entirety. But we would appreciate it now if you would give us a summary and whatever introductory comments you may wish to make.

STATEMENT OF DR. ANDREW C. VON ESCHENBACH

Dr. VON ESCHENBACH. Thank you, Mr. Chairman.

Good morning, Senator Kohl. And good morning, Senator Craig, and other members of the staff.

I am very honored to be here as the acting Commissioner of the Food and Drug Administration to present this 2007 fiscal year budget. But most of all, to also have the opportunity to thank you for the continued support and commitment that you have made to the FDA in helping to assure that it continues to be the gold standard around the world for the safety and effectiveness of the interventions that we provide to people.

Our 2007 budget request proposes a total budget of \$1.95 billion, of which \$1.54 billion is in discretionary budget authority and \$402 million will be in user fees from the firms that we regulate. These funds are precious, and they are, in fact, essential to FDA's continuing effort to assure that Americans can go to bed each night confident that the food they ate is safe, the medical devices they use are reliable, and the drugs that they gave to their children and grandchildren were safe and effective.

As we developed this 2007 proposal, the first thing we focused on was FDA's most precious asset, its people. The funds we are requesting are essential for us to continue to recruit, retain, and nurture a critical and diversified staff of highly skilled professionals and scientists who make it possible for the FDA to achieve the gold standard in regulating foods, drugs, and medical products.

Our request includes \$20 million for cost of living increases that are essential to meet payroll obligations and needed funds for the infrastructure to support our workforce and consolidate FDA operations in modern facilities at White Oak.

In addition to the workforce-related issues, we have also focused on emerging urgent public health challenges and opportunities. The increase of \$30.5 million over fiscal year 2006 for pandemic preparedness is for a comprehensive program that is designed to safeguard Americans from the danger of avian flu by enhancing and integrating our programs across vaccine development, antivirals, enhancement of devices for detection as well as for human protection, and also include issues with regard to animal welfare and human health.

The \$20 million for food defense is to protect the Nation's food supply both from intentional terrorist attacks as well as to enhance our ability to safeguard the food supply from unintentional contamination.

\$4 million for human drug safety, plus an additional \$700,000 in user fees, we believe will strengthen our capacity to recognize and act upon emerging drug safety concerns. And the \$2.5 million for human tissue safety is in response to the dramatic growth that we are experiencing in the use of tissues for transplantation and the anticipation of the emerging challenges that will come from tissues obtained through bioengineering.

With regard to the request for \$6 million for the Critical Path to Personalized Medicine, this initiative is an essential investment, an investment in FDA's ability to respond to the explosion in molecular medicine that is responsible for and resulting in progress toward new treatments, diagnostics, and preventive interventions.

By using the science and technology of the 21st century, Critical Path will help ensure that FDA can guide these new discoveries

through the development process so that they are able to be delivered to patients in a rapid, safe, and effective manner.

A modern, robust Critical Path will lead to solutions that will deliver on the promise of making our future health care personalized, predictive, preemptive, and, in fact, more cost effective.

As you have indicated, to partially offset the cost of these initiatives and, most importantly, as good stewards of the resources that you have already provided, FDA has undergone a process to identify and an activities for opportunities for efficiencies and proposes to strategically redeploy \$52 million in base funds.

We have done this, first and foremost, with the principle to not undermine or impair our commitment to public health. But we believe by looking at opportunities within the portfolio to determine where there are programs that could be effectively carried out by alternative or other strategies, where there are opportunities to eliminate waste and maximize the impact of our investment, we believe that we can modernize and transform our business operations, as well as our programmatic operations, to address the emerging needs of the 21st century.

We will accomplish this strategic redeployment while assuring you that we will maintain our century-old commitment to assuring the health and welfare of the American public.

There are two new user fees that are being proposed. One covers the cost of re-inspecting facilities that fail to meet standards, and the second would cover the cost of issuing food and animal feed export certificates.

As you have pointed out, the investment in the FDA in this budget is investment in the future of our country and our commitment to continue to ensure the health and safety of the American public. We propose to use these resources wisely and carefully as good stewards and, in doing so, assure a healthier America for generations to come.

PREPARED STATEMENT

We really are grateful and appreciate your commitment and your interest to working together with us, as we will with you, to be sure that we fulfill that goal.

[The statement follows:]

PREPARED STATEMENT OF DR. ANDREW C. VON ESCHENBACH

Introduction

Good morning Chairman Bennett, Senator Kohl, and distinguished members of the Subcommittee. I am very honored to have been appointed by President Bush 6 months ago as Acting Commissioner of the FDA, and I consider it a privilege to present our fiscal year 2007 budget request on behalf of this extraordinary agency. I am joined today by Ms. Kathy Heuer, FDA's Chief Financial Officer and Associate Commissioner for Management, and Mr. Richard Turman, Deputy Assistant Secretary for Budget, Technology, and Finance of the Department of Health and Human Services (DHHS). I also have members of FDA's senior leadership with me at today's hearing.

Last September, President Bush selected me to lead an agency to which I appreciate, we, as Americans owe a great debt of gratitude. Millions of Americans go to sleep each night, secure in the knowledge that the food they ate and the medicines they gave their child were safe and effective. They do so, thanks to the thousands of dedicated professionals at FDA who work to assure the safety, efficacy, and security of drugs, vaccines and biological products, medical devices, our Nation's food supply, and other consumer products.

This year, the Food and Drug Administration will celebrate its 100th birthday, marking a century as America's gold standard for safety and consumer protection. We began in 1906, when Congress passed and President Theodore Roosevelt signed the Food and Drugs Act. This statute entrusted the Bureau of Chemistry, an office in the U.S. Department of Agriculture, to implement the sweeping new law. The Bureau eventually became the FDA, an agency of the Department of Health and Human Services. As the first consumer protection agency in the United States, FDA has a distinguished record, established during its 100 years of service to the American public.

Today, the products we regulate represent almost 25 percent of U.S. consumer spending and include 80 percent of our food supply and all human drugs, vaccines, medical devices, tissues for transplantation, equipment that emits radiation, cosmetics, and animal drugs and feed. FDA takes great pride in its heritage and accomplishments, promoting and protecting the health and well-being of all Americans.

I assure you that the precious resources you provide this agency in fiscal year 2007 will be used wisely and judiciously to ensure that we maintain this record of excellence, as well as work to respond to the growing challenges to advance the Nation's public health in a new era of rapidly developing science and individualized medicine.

I want to thank the Subcommittee members for providing FDA with several key increases in the fiscal year 2006 appropriation. The Subcommittee demonstrated its commitment to FDA's mission by providing increases for drug safety, the Critical Path Initiative, review of direct-to-consumer advertising, Food Defense, medical device review, and the FDA consolidation project at White Oak, Maryland. In addition to the amounts in the annual appropriations bill, I also want to express my thanks to Congress for the supplemental appropriation of \$20 million to contribute to our Nation's preparedness for the threat of pandemic flu. FDA enters this appropriation cycle mindful of our responsibility and stewardship, and that all Federal agencies must operate in an environment where our dollars must go to the greatest need.

FDA's 2007 President's Budget Request

In our fiscal year 2007 budget, the Administration proposes a total program level for the FDA budget of \$1.95 billion, an increase of 3.8 percent above the fiscal year 2006 amount. This includes \$1.54 billion in discretionary budget authority and \$402 million in current law user fees. Our budget also includes \$25.5 million for two new user fees. Our budget request maintains critically important core functions and demonstrates that our programs meet a firm test of accountability. At the same time, we are heeding the President's call to assure continued progress by fostering innovation and focusing on emerging priorities. In fiscal year 2007, FDA will employ resources to advance its mission to protect the public health by assuring the quality of food and medical supplies and by implementing advanced technologies to monitor and speed innovations to market that will make foods safer and medical products more effective, safer, and more affordable. We will also implement advanced tools to ensure that the medical community can use molecular biology to improve outcomes for patients. We must accomplish these goals in a way that provides the public with the accurate, science-based information they need to use food and medicine to improve their health.

The President's budget focuses on six emerging, and urgent challenges and opportunities. To address these challenges, the budget proposal increases funding in these targeted activities above the amount provided in fiscal year 2006: \$30.5 million for Pandemic Preparedness, \$19.9 million for Food Defense, \$5.9 million for the Critical Path to Personalized Medicine, \$4.0 million for Human Drug Safety (plus an additional \$0.7 million in user fees), \$2.5 million for Human Tissue Safety, and \$7.4 million to meet the statutory triggers of the Animal Drug and Medical Device user fee programs. In addition to these high priority initiatives, the budget requests \$20.3 million for inflationary cost-of-living increases that will enable the agency to recruit, nurture, and retain a critical mass of highly skilled professionals and scientists. This dedicated staff is necessary to respond to greater challenges in the regulatory process, including increased complexity of the sciences and technology and the need for a more rapid pace.

FDA also seeks \$1.2 million for the Unified Financial Management System, and an investment of \$14.3 million for the agency's infrastructure needs. To partially offset the cost of these initiatives, the President's budget proposes to strategically redeploy \$52.3 million in base funds. Even in an era of declining budgets, FDA recognizes the need to modernize and transform operations to address the emerging needs of the 21st century. Therefore, we engaged in an ongoing process to strategically redeploy resources to address high-risk public health challenges while main-

taining our century-old commitment to principles that have made us the world's "gold standard" for regulating food and medical products. In doing so, the proposed budget will permit FDA to meet its ongoing statutory and regulatory responsibilities, while allowing us to initiate new and expanded efforts in critical areas of our mission. Now I would like to provide you with greater detail on our proposed budget increases.

Pandemic Preparedness (+\$30.5 million)

To safeguard Americans from the danger of pandemic influenza, FDA requests a total base program of \$55.3 million in fiscal year 2007. This amount is \$30.5 million more than the fiscal year 2006 enacted level, which includes the \$20 million in supplemental appropriations provided by Public Law 109-148. The supplemental will allow FDA to rebuild and enhance its infrastructure; provide personnel and expertise in the essential clinical, product and manufacturing areas necessary to support new vaccine development for pandemic influenza. With the fiscal year 2007 funds, we will conduct a more comprehensive program to prepare for and respond to the risks of a pandemic flu outbreak. The resources will build upon the program this Congress launched in the supplemental, and will allow FDA to:

- Engage in public-private partnerships to select, prepare, and test pandemic seed strains of variants of the H5N1 virus.
- Develop reagents (used to assess vaccine potency) that are essential for successful large-scale manufacturing.
- Evaluate and license flu vaccines that rely on current egg-based technology as well as encouraging the development of new approaches such as cell culture-based vaccines, recombinant vaccines, and vaccines that contain adjuvants—substances added to vaccines to stimulate an immune response.
- Provide essential technical support to vaccine manufacturers throughout the vaccine development process, including support throughout the manufacturing phase.
- Develop analytical methods to detect, identify, and quantify antiviral residues in poultry, so that these drugs do not promote drug resistance in humans.
- Develop and validate methods to detect avian influenza in foods and advise American consumers about how to safely handle and cook these foods.

We make this request because public health experts tell us that the risks of being unprepared for a pandemic could mean the death of up to 200,000 Americans (based on a medium-level pandemic scenario) and economic losses of up to \$160 billion. In the near term, our pandemic initiative will stimulate broader interest among vaccine manufacturers, as they recognize that FDA will provide consistent technical support to overcome vaccine development hurdles. We have already seen results in this area. In the longer term, our fiscal year 2007 investment will yield essential seed strains and reagents, and allow us to transfer this technology to manufacturers, while we also perform our regulatory responsibilities of evaluating and licensing pandemic influenza vaccine products. Over the next 2–4 years, we will also fulfill our public health responsibilities related to foods and veterinary products, by delivering methods to detect antiviral residues and by educating Americans about safe food practices.

Food Defense (+\$20 million)

FDA seeks an investment of an additional \$20 million in fiscal year 2007 to protect the Nation's food supply from terrorist attack, by developing and deploying improved methods to screen food and feed imports and expanding the Food Emergency Response Network (FERN).

FERN is a network of Federal and State laboratories designed to ensure that we have the analytic surge capacity to respond to an attack on the food system. By the end of fiscal year 2006, we plan to have an operational FERN system of 10 Federal and 10 State labs. The fiscal year 2007 funds (\$13 million) will allow FDA to expand the current network by six additional labs, located at existing State facilities, and we will work to bring these on-line before the end of the fiscal year. We will fully equip these new labs, and provide operational funding and technical assistance so that they can conduct food defense activities. Our technical assistance will include proficiency testing on the new equipment and training to validate their ability to conduct food testing in response to an emergency. The result of this investment will be a more robust and more geographically diverse capability to provide the essential surge capacity to test contaminated food samples and allow us to warn the public about threats to the food supply. By working cooperatively with State facilities, we can stretch our Federal dollars and strengthen food defense at the Federal and State level.

Within the \$20 million increase, we will also:

- Conduct food defense research (\$1 million) to fill in gap areas that we identified in the vulnerability assessments we conducted on 23 major food products such as baby food, infant formula, dairy products, soft drinks, and bottled water.
- Strengthen the Electronic Laboratory Exchange Network (eLEXNET), an Internet based data exchange system used by Federal, State, and local government food safety laboratories. Using fiscal year 2007 funds, we will use eLEXNET to provide food sector-specific information to sister agencies and build a secure interface so that we can exchange data with DHS. Finally, we will purchase essential reagents and test kits to conduct biomonitoring surveillance. In fiscal year 2007, we will spend \$2 million of the Food Defense increase for these activities.
- Improve our Emergency Operations Network (\$1 million) to allow FDA to conduct more sophisticated incident tracking for food-related emergencies.
- Continue Field support of food defense operations (\$3 million), including the targeting of potentially high-risk imported foods through Prior Notice Import Security Reviews based on intelligence, FDA inspection reports, discrepancies in prior notice reporting and sample collection and analysis.

Critical Path to Personalized Medicine (+ \$5.9 million)

FDA requests an increase of \$5.9 million in fiscal year 2007 for the Critical Path to Personalized Medicine initiative. This will allow us to increase the predictability and efficiency of developing new medical products, and deliver greater benefits to patients as we accelerate the field of personalized, predictive, preemptive, and participatory medicine. Our goal is to stimulate a new generation of scientific tools that will enable product sponsors to evaluate and predict the safety and effectiveness of drugs. This will permit physicians to tailor therapies to individual patients and avoid potentially dangerous adverse events. The Critical Path to Personalized Medicine Initiative also fulfills the Congress' expectation under the Food and Drug Administration Modernization Act, when it charged FDA to work collaboratively with partners in government, academia, and industry to advance medical product development. A modern, robust Critical Path will lead to solutions that will deliver on the promise to make our future health care, personalized, predictive, preemptive, and more cost effective.

The fiscal year 2007 investment will support:

- Imaging Initiative.*—Our Critical Path investment will support efforts to accelerate an understanding of the use of positron emission tomography (PET) and other advanced imaging technologies as surrogate endpoints for developing new cancer drugs. A surrogate endpoint helps to predict the benefit that a patient may experience from therapy. In fiscal year 2007, we will participate in developing technical standards for PET imaging—the tools that will enable drug developers to evaluate and improve the effectiveness of new products.
- Improving Stent Design.*—Cardiovascular disease is a significant cause of morbidity and mortality in the United States, and drug eluting stents have become a standard therapy to address cardiac disease in many patients. Today, most vascular stents eventually fail and alternative designs are difficult to test in humans. Our objective is to improve stent performance and safety by predicting and avoiding product failures. In fiscal year 2007, we will develop the preliminary components of a simulation model of drug eluting stent behavior in adults and children. Also in fiscal year 2007, we will work to develop open source imaging software to assess stent performance and begin to develop guidance for industry on using the simulation model to predict stent performance.
- ECG Warehouse.*—We will invest funds to develop the tools to permit searches of electrocardiogram (ECG) data submitted with drug applications so that we can identify cardiovascular risk patterns associated with unsafe drugs. We will also partner with academia and the public sector in fiscal year 2007 to conduct additional ECG analyses. This will improve our ability to identify cardiac safety concerns before we approve a drug for marketing and also detect post market safety signals. Through these activities, we will help ensure that therapies are safe and effective, and we will improve outcomes for patients who are using products that are already on the market.

The need for new medical treatments and the investment of billions of dollars in basic biomedical research led many in the medical community to anticipate a new wave of medical products capable of dramatically saving and extending lives. Yet the recent slowdown in the rate of new medical treatments actually reaching patients is a significant concern at FDA. Products fail before they reach the market because clinical trials fail to demonstrate safety or efficacy, or they cannot be manufactured at a consistently high quality. Despite recent innovations, many serious and life-threatening diseases still lack effective treatments.

At FDA, we witness the full spectrum of drug, device, and biologic product development. From this unique perspective, it is clear that the development of evaluative scientific tools to utilize in medical product development has not kept pace with the rapid advances in basic sciences. The path from cutting-edge medical discovery to the delivery of safe and effective treatments is long, arduous, and uncertain—and it does not yield extensive information on product performance. To correct this imbalance, FDA initiated the Critical Path to Personalized Medicine, a program designed to modernize medical product development to ensure more efficient and more informative product development and clinical use. FDA considers the Critical Path Initiative to be its top scientific policy initiative for at least the next 5 years.

FDA's Critical Path Initiative will stimulate research community efforts to identify the essential biomarkers and improved clinical trial designs that will accelerate product development. Biomarkers are measurable characteristics that reflect physiological or disease processes. Medicine can use biomarkers to predict or monitor response to therapy. The initiative will generate essential information to identify patients likely to benefit from a treatment and patients more likely to respond adversely to a product. Without clinically proven biomarkers and innovative trial designs, we cannot modernize medical product development and realize the potential of personalized medicine. The subcommittee recognized this need when it appropriated funds for FDA in fiscal year 2006 to study cardiovascular biomarkers predictive of safety and clinical outcomes, and the funds that we request in fiscal year 2007 will support broader efforts to achieve personalized medicine.

Drug Safety (+\$4.7 million in budget authority and user fees)

FDA will build on recent improvements to its drug safety activities with an fiscal year 2007 increase of \$4.7 million (a \$3.96 million increase in budget authority and \$0.74 million in PDUFA user fees). The proposed fiscal year 2007 budget will provide a significant increase to our base resources for drug safety and will allow FDA to continue to strengthen our capacity to recognize and act on emerging drug safety concerns.

As we plan for fiscal year 2007, we must continue to focus on the needs of the patient. We must constantly ask ourselves—how can we achieve the proper risk/benefit balance while speeding patient access to safe and effective products? U.S. pharmacies fill approximately 3.7 billion prescriptions per year and consumers make more than 5 billion over-the-counter drug purchases annually. The effect of these medicines on the full spectrum of our population causes unforeseen problems to surface that may not have appeared during the sometimes-lengthy drug review process.

Our fiscal year 2007 drug safety request will permit us to launch a web-based system that provides agency analysts faster access to adverse event reports. Known as AERS II, this system will allow FDA to more easily evaluate potential safety issues, and improve our ability to take follow-up actions to protect patients. Fiscal year 2007 funding will also allow us to analyze valuable drug safety information housed in CMS and other population-based databases and to conduct studies of high priority safety issues in the Medicare population. Studies conducted on these types of databases will provide more supporting evidence about drug use under a broader range of conditions, and more detailed evidence about drug safety in subgroups of patients, such as the elderly, and in patients with multiple medical conditions. This will provide FDA with many of the tools necessary to formulate and communicate safety information to health care practitioners, consumers, and the research community in a more timely and user-friendly way.

We have made important drug safety enhancements during the past year, and I would like to highlight these activities for your now. The members of this Subcommittee provided an increase of \$9.9 million in FDA's fiscal year 2006 budget. We will bolster premarket and postmarket drug safety functions by using these funds to:

- Increase the professional staff in FDA's Center for Drug Evaluation and Research (CDER) who perform high priority drug safety reviews.
- Increase the number of staff with expertise in critical areas, such as risk management, risk communication, and epidemiology.
- Expand our information technology infrastructure for monitoring post-marketing data by increasing access to a wide range of clinical, pharmacy, and administrative databases.
- Hire additional experts to enhance use of multidisciplinary, multi-office teams to interpret drug safety data.
- Access external population-based "linked" databases to identify drug safety signals.

Other important drug safety accomplishments during the past year include:

- Establishing a Drug Safety Oversight Board to provide independent oversight and advice on drug safety and disseminating safety information. The Board conducted 5 meetings in 2005 to discuss 17 drug products with potential risks.
- Appointing a new director of CDER's Office of Drug Safety.
- Conducting a public meeting of experts to assess risk communication about drugs and to plan future communication efforts.
- Unveiling a major revision to the format of prescription drug information, commonly called the package insert, to give healthcare professionals clear and concise prescribing information.

These efforts emphasize our commitment to providing the American public with safe and effective medical products.

Tissue Safety (+\$2.5 million)

FDA requests an increase of \$2.5 million to provide the essential resources to support a human tissue safety, including our role in monitoring the expanding field of tissue transplantation and the emerging challenges of bioengineering. These funds will allow the agency to:

- Commence a comprehensive risk-based approach to assure the safety and quality of human cells, tissues and cellular and tissue-based products used for transplantation. Examples include corneas, heart valves, ligaments, joints, skin, or other tissues.
- Promptly monitor and investigate adverse events and tissue product problems.
- Take early action to improve tissue practices and prevent tissue-related injuries and deaths.
- Educate industry, the medical community, and the public about human tissue safety.
- Support promising new technologies that use cells and tissues, including therapies for diseases such as cancer, AIDS, Parkinson's disease, hemophilia, diabetes, and other serious conditions.

This program will provide guidance and predictability to more than 2,000 registered establishments that process and distribute tissue products used in medical procedures that save or enhance the lives of recipients. FDA has seen its workload in the area of human tissue transplants rise dramatically as transplants have increased from approximately 350,000 in 1990, to more than 1,000,000 annually. The number of transplants will continue to rise in the years ahead.

With these resources, FDA will conduct 75 additional tissue inspections in fiscal year 2007 and thereby increase our annual inspection coverage to 325 facilities. Through inspection and monitoring activities, we can ensure that establishments demonstrate safety and efficacy of their products. These funds will also permit FDA to rapidly review, track, and analyze tissue deviation reports. Finally, we will issue guidance for industry on emerging issues relating to the eligibility of donors and good tissue practices. The goal of these efforts is to ensure safe outcomes for patients when they receive tissue transplants.

FDA's announcement in early February that we ordered a New Jersey company to cease operations is evidence that we will take action to protect the public health against tissue manufacturers that fail to follow safety requirements. This is an example of the targeted enforcement action we will conduct to protect the public health when we have evidence unsafe tissue practices.

Budget Authority in Support of User Fee Programs—MDUFMA and ADUFA (+\$7.4 million)

To achieve more timely and cost-effective review of new medical devices and animal drugs, we continue to implement Medical Device User Fee and Modernization Act (MDUFMA) and the Animal Drug User Fee Act (ADUFA). Congress enacted these statutes to allow the agency to collect user fees from companies that submit medical device and animal drug applications.

In fiscal year 2007, we are requesting a total increase of \$7.4 million in new budget authority (\$4.9 million for medical devices and \$2.5 million for animal drugs) to ensure that we meet statutory requirements, known as triggers, and fulfill the fiscal year 2007 performance commitments under these programs. If we do not receive sufficient budget authority to meet the statutory triggers, FDA will lose the right to collect \$55.3 million in user fees. The flow of potentially life saving medical devices will decline and the use of unapproved drugs in food-producing animals will likely rise.

Under both these user fee programs, we pursue a complex and comprehensive set of product review goals. Each year brings additional goals, and the goals become more aggressive. FDA provides a complete report on its performance on under these programs at the end of each year.

The proposed increase will permit FDA to maintain its highly skilled scientific and professional review staff and conduct speedier review and approval of safe and effective medical devices. Under MDUFMA, FDA is meeting, or is on track to meet, nearly all of the performance goals for fiscal year 2003, fiscal year 2004, and fiscal year 2005. We will continue to make program improvements to ensure we meet the goals for fiscal year 2006 and fiscal year 2007. Under ADUFA, FDA expects to meet or exceed all performance goals.

Cost of Living—Paying our People (+\$20.3 million)

Soon after the President appointed me Acting Commissioner, I told my FDA colleagues that the well-being of our agency's employees was one of my top priorities. The talented and dedicated FDA employees are the agency's most precious asset and are the primary reason for our success.

The proposed increase of \$20.3 million to meet inflationary pay costs is essential to FDA's ability to accomplish its public health mission. Payroll costs account for more than 60-percent of the FDA budget, and the Agency is not able to absorb inflationary increases on such a significant portion of its resources. These funds will allow FDA to maintain its world-class workforce and achieve the promise of a healthier America.

FDA's diverse portfolio of public health responsibilities demands that we maintain a large cadre of scientists and professionals with the training and experience to respond to complex and escalating public health challenges. This workforce is directly engaged in both developing the science of regulation as well as administering regulatory functions.

FDA professionals are increasingly challenged by evolving food defense responsibilities as well as growing responsibilities in regulation of vaccine, drug, and device, development. Within the past year, they have addressed threats such as BSE (Mad Cow Disease), Salmonella, West Nile Virus, and pandemic flu. The FDA workforce reviews, approves, and continues to ensure the safety and effectiveness of products to manage cancer, diabetes, and heart disease, as well as oversee products intended to preserve health. FDA principally expends its budget for payroll that allows us to recruit and retain a skilled workforce dedicated to safeguarding the public using advanced tools to preempt public health threats.

Unified Financial Management System (UFMS) (+\$1.2 million)

In fiscal year 2007, FDA seeks an increase of \$1.2 million to fully utilize the Unified Financial Management System (UFMS) for all of our financial transactions. These funds will allow FDA to achieve a major program milestone in the implementation of a new centralized financial management system under the Department of Health and Human Services (HHS). These additional funds would bring the fiscal year funding level to \$14.1 million.

UFMS is changing the way HHS agencies do business as it improves efficiencies in business processes and technology. It will replace five redundant and outdated accounting systems in use at the National Institutes of Health, the FDA, the CDC, the Centers for Medicare and Medicaid Services, and the DHHS Program Support Center. The requested increase and the base funds in our budget will support dual functions. First, as a component of the Department-wide system, FDA resources will support testing and integration of the UFMS system, as well as regular operation and maintenance of UFMS. Second, fiscal year 2007 funding will support FDA-specific functions such as the purchase of reporting tools and software licenses, essential system upgrades and new software releases, and training to support FDA users of this new system. This will ensure that we satisfy financial requirements and provide timely financial information to executives and managers to support better decision making. As FDA fully integrates UFMS into our systems and way of doing business throughout fiscal year 2007, we expect to witness the projected efficiencies for this vital enterprise and be able to use UFMS' full financial management capability.

Infrastructure (+\$11.3 million)

In fiscal year 2007, FDA submits a modest request to fund three fundamental components of our physical infrastructure:

- An increase of \$10.5 million for rent payments to the General Services Administration (GSA).
- An increase of \$3.8 million in budget authority to maintain progress on the White Oak Consolidation project.
- A reduction of nearly \$3 million below the fiscal year 2006 appropriated level for our Buildings and Facilities account.

In total, these proposals would result in a net increase of \$11.3 million for fiscal year 2007.

We also plan to commit \$8.2 million in PDUFA carryover funds to the White Oak project and \$1.9 million for GSA rental payments. FDA continues to seek support for the White Oak project with the goal of eventually housing over 7,700 staff in 2.3 million square feet of space. As of the end of calendar year 2005, we have approximately 1,850 staff on site at White Oak, in three buildings with almost 700,000 square feet. The new buildings will eventually replace all 40 existing, fragmented facilities in 16 locations that support the Office of the Commissioner, and all of our Centers and the Field headquarters, other than the Center for Food Safety and Applied Nutrition and the National Center for Toxicological Research.

Proposed User Fees: Reinspection and Food/Animal Drug Export Certificates (\$25.5 million)

In addition to those user fees authorized by statute, the FDA is proposing two new user fees. The first, estimated at \$22.0 million, would pay the full cost of reinspection and other FDA follow-up work if a manufacturer fails to meet important FDA requirements such as Good Manufacturing Practices, which help ensure high quality and safety of FDA regulated products. When a firm fails an inspection, FDA must conduct a reinspection and perform associated laboratory analysis to verify the firm's corrective measures.

The reinspection user fee will ensure that facilities that fail to comply with established health and safety standards bear the cost of FDA follow-up inspection. We are asking Congress to assess the cost of follow-up inspections on those who fail to comply, rather than on the American taxpayer, who bears the cost today. The natural consequence of this change will be that manufacturers will work to ensure that they meet established standards.

The second proposed new user fee will cover the cost of issuing an approximately 37,000 food and animal feed export certificates. We have estimated the cost of this user fee program at \$3.5 million. Although the agency's effort to issue these certificates benefits industry exports, FDA must support this function at the cost of other vital public health activities. FDA's proposal for user fees would establish a source of dedicated funding for this activity and allow the agency to better perform this function. The domestic food and animal feed industry would benefit from the agency's enhanced ability to facilitate the exportation of their products.

The Federal Food, Drug, and Cosmetic Act (the Act) authorizes FDA to collect user fees for export certificates for human drugs, animal drugs, and devices. However, this authority does not extend to collecting user fees for export certificates for foods and animal feed. FDA expends significant resources annually to issue these certificates, and the agency needs to focus its resources on activities that are central to its public health mission. The Administration has asked that Congress fund these two user fee programs with mandatory budget authority.

Current Law User Fees (+ \$20.2 million)

We are also requesting an increase of \$20.2 million for user fees that support prescription drug review, medical device review, animal drug review, mammography inspections, export certification, and color certification fees, for a total fiscal year 2007 user fee level of \$402 million. These fees enable FDA to review medical products in a timely manner and reimburse FDA for two services (color certification and export certification for human drugs, animal drugs, and devices) that we provide to industry. All of these requested fee increases are authorized under current law. In fiscal year 2007, FDA will work with Congress on the reauthorization of the PDUFA, MDUFA, and ADUFA user fee programs.

Closing

Mr. Chairman, I look forward to working with you, members of the Subcommittee, and your staffs to maximize FDA's resources in the best interest of the American people and our country as we move into fiscal year 2007. The agency's program level request of \$1.95 billion is necessary to perform our mission—established by Congress a Century ago—to protect and promote the health and safety of the American public. At the Food and Drug Administration, we work tirelessly to fulfill these public health responsibilities. Our goal is to maximize the benefits and minimize the risks from the products we regulate.

Among my highest priorities as Acting Commissioner—for as long I am privileged to serve at the helm of FDA—will be to foster the development of the FDA of the 21st Century. Building on the success of the past, we will maintain our "covenant of trust" with patients and the public. We will assure they have safe, effective, modern, and cost efficient solutions for the challenges to their health and well-being, and the health and well-being of their children and grandchildren. A well managed and adequately funded FDA will mean a healthier America for many generations to come.

STRATEGIC REDEPLOYMENT

Senator BENNETT. Thank you very much.

You talk about reprogramming and redirecting the \$52 million. Would you please provide for the record more specific information on each program that you plan to either reduce or eliminate and the impact this will have?

Dr. VON ESCHENBACH. Yes, sir. We will be very pleased to provide that for the record in significant detail.

[The information follows:]

Food and Drug Administration
Center for Drug Evaluation and Research FY 2007 Strategic Redeployment
(in Thousands)

Program	FY2006 Enacted	Strategic Redeployment	Program Increases	FY2007
Center for Drug Evaluation and Research	\$217,797	\$5,430	\$12,842	\$225,209

Program Areas	Redeployment Amount			FTE	Strategy
	BASE PROGRAM \$	AMOUNT REDEPLOYED \$	FTE BASE		
To fund FY 2007 priority initiatives such as Drug Safety and the Critical Path to Personalized Medicine, FDA re-deployed resources from base programs.					
Generic Drug Research Contracts	\$200	\$200	N/A	N/A	We will not cut resources for generic drug review functions. In fact, our current spending exceeds our Congressional earmark. We will pursue other methods to identify bioequivalence standards for novel dosage forms. We will also pursue leveraging through cooperative research agreements and by working with industry, consistent with the objectives of the Critical Path initiative.
Research Activities -- Attrition and Lab Support	\$5,750	\$841	36	4	We will apply a risk-based approach to our research activities, focusing on the highest priority issues and leveraging activities through the Critical Path Initiative. We will explore opportunities to partner with other Department and other Government agencies and coordinate with external industry partners where possible. We will seek innovative ways to maintain our labs through cost savings and other strategies.
Center wide administrative services and support -- includes communications, staff management, and FOI support	\$20,051	\$2,860	130	10	We will continue to apply our best practices for managing the volume and complexity of FOI requests, continuing to identify and implement additional efficiencies where possible. We will leverage Center best practices for providing administrative and support services. We will continue efforts to consolidate programmatic functions and streamline operations to ensure that mission-critical functions continue effectively.
Information Technology Infrastructure	\$1,700	\$1,379	N/A	N/A	We will seek to leverage our existing information systems processing and computing equipment and partnering with other Agency Centers/Offices to support Center programs by consolidating applications on existing servers and by applying best practices for managing our infrastructure and seeking more cost effective methods for providing IT support services.
Information Technology Infrastructure (Generic Drugs Program)		\$150	N/A	N/A	We will not cut resources for generic drug review functions. We will make every effort to leverage our existing information systems processing and computing equipment and partner with other FDA Centers/Offices to support the generic drugs program.
Total	\$ 27,701	5,430	166	14	

Food and Drug Administration
Center for Biologics Evaluation and Research FY 2007 Strategic Redeployment
(In Thousands)

Program	FY2006 Enacted	Strategic Redeployment	Program Increases	FY2007
Center for Biologics Evaluation and Research	\$111,832	\$7,568	\$17,542	\$121,806

Program Areas	Redeployment Amount			Strategy	
	BASE PROGRAM \$	AMOUNT REDEPLOYED \$	FTE BASE	FTE	For Meeting Public Health Commitment
Guidance Development	\$2,593	\$1,400	22	6	CBER will develop guidances that offer the greatest impact on product development and on product areas that have public health and patient safety benefits. Efforts to provide outreach and guidance to encourage and orient specific product development will increase efficiencies in review. CBER will also work with stakeholders to identify opportunities for outside parties to develop and submit draft guidance for consideration.
Interactions with Sponsors	\$154	\$70	1	0	CBER will concentrate its resources to facilitate the development of biological products to meet unmet needs. CBER will also optimize its business process to increase productivity from our early interactions with product sponsors. CBER will utilize information technology enhancements to improve the efficiency of review and product testing. CBER will use science-led interactions with sponsors to guide the development process. CBER will also leverage activities with NIH and other HHS partners.
Communications and Outreach	\$1,051	\$500	9	2	CBER will focus on consumer and patient information resources on areas with immediate consumer interest and health impacts. CBER will also engage in leveraging of communications with CDC and others in areas such as vaccines, blood and tissues. CBER will concentrate its industry outreach resources to facilitate the development of biological products of high public health benefit. CBER will use coordinated outreach activities with public health communication through interactions with NIH and CDC. CBER will focus on communication and outreach activities to encourage and orient specific product development using internal based activities for more cost-effective training.
Blood Program	\$7,709	\$1,300	66	5	CBER will increase internal coordination and prioritization activities to enhance efficiency and increase its collaboration with DHHS, CDC & NIH, to help take appropriate and efficient actions to address emerging threats to the blood supply, encourage development of digital diagnostic methods, issue critical and urgent standards and regulatory controls, and issue critical guidances. Recent successful interactions include those with CDC and industry to develop diagnostic tests and standards to screen blood donors for West Nile Virus, with plasma industry to develop technical standards for plasma-derived products, and, with AABB and the blood industry to respond to disasters and ET events. To assist in a rapid response, CBER will enhance the focus and efficiency of its involvement in the international arena including thorough information sharing, coordination and harmonization of product development, evaluation and quality standards and efforts. CBER will partner with others to provide needed samples, assays, standards and reagents.

Food and Drug Administration
Center for Biologics Evaluation and Research FY 2007 Strategic Redeployment
(In Thousands)

Program Areas	Redeployment Amount			Strategy
	BASE PROGRAM \$	AMOUNT REDEPLOYED \$	FTE BASE FTE	
Cell and Gene Therapy Program	\$2,099	\$603	18	For Meeting Public Health Commitment Cell and gene therapies are rapidly evolving therapies with little precedent for the critical path to licensure. There are extremely promising products that are likely to come to clinical fruition in the near future, for example cord blood for malignancies and islet cells for diabetes. We will focus on reducing the number while increasing the quality and efficiency of meetings, including informal communications with academic and industry sponsors, workshops and communications as well as guidance development. We will focus workshops and outreach efforts on public health and safety issues, and on products that meet otherwise unmet needs and appear most promising. We will work increasingly with NIH and other stakeholders to leverage time and resources.
Postmarket and Product Safety	\$4,205	\$1,100	36	CBER will deal with its safety and compliance activities by acting on issues with public health risk and urgency. CBER will utilize information technology enhancements to improve post-marketing and manufacturing surveillance activities. To handle the offsets, we will deal with our safety and compliance activities by acting on all issues in order of risk and priority. Certain preventive and outreach activities will be deferred. We will limit the collection and analysis of some surveillance data and information (e.g. biological product deviation reports, recalls and their use to identify and track trends in quality and other reported manufacturing events). We will target our clinical trial and product development compliance activity operations to the highest priority, highest risk product areas.
Research	\$4,135	\$1,600	35	CBER will leverage efforts with NIH, CDC and other stakeholders and concentrate its resources to facilitate the development, and assure the safety and effectiveness, of biological products having public health priority/need. In the areas of blood and blood products, vaccines, tissues and tissue engineering and cell and gene therapies. Increased use of public-private collaboration and critical path science investments offer the potential of increased leveraging of resources. Laboratory quality, mission management and IT systems in product testing will improve efficiency and quality.
International Harmonization	\$2,943	\$995	25	CBER will concentrate its international activities on areas with the most direct public health, product availability, and quality impact through strategic positioning and focus, reducing overall resource use. CBER will work to enhance global product specific surveillance, information sharing, harmonization and intervention capacities for blood, vaccine and tissue products.
Total	\$24,859	\$7,568	212	30

Food and Drug Administration
Center for Veterinary Medicine FY 2007 Strategic Redeployment
(In Thousands)

Program	FY2006 Enacted	Strategic Redeployment	Program Increases	FY2007
Center for Veterinary Medicine	\$54,739	\$1,469	\$6,446	\$59,716

Program Areas	Redeployment Amount				FTE	Strategy
	BASE PROGRAM \$	AMOUNT REDEPLOYED \$	FTE BASE			
To fund FY 2007 priority initiatives such as Pandemic Preparedness, FDA re-deployed resources from base programs.						
Plant Biotechnology Activities	\$192	\$192	1		1	CVM will no longer provide industry support for voluntary activities related to plant biotechnology and participation in organizations outside of FDA relating to plant biotechnology. CFSAN will assume responsibility for this program and maintain current efforts to protect the public health.
Milk Safety Activities	\$188	\$188	0		0	CVM will no longer participate in the milk drug residue activities in the Agency. CFSAN will assume responsibility for this program and maintain current efforts to protect the public health.
Research Activities	\$3,245	\$792	20		1	CVM will reduce research efforts to support approval of drugs for minor use/minor species. Instead of developing data for several fish species, CVM would limit the research to one or two species of most commercial interest. CVM will curtail the development and standardization of tests methods for antimicrobial susceptibility and drug residues and will collaborate with academic and EU government laboratories for support. CVM would reduce retail meat surveillance related activities and will collaborate with state public health laboratories for support.
GRAS (simplified notification system)	\$297	\$297	0		0	CVM will not implement the GRAS simplified notification system for use in deciding on the marketing of non-drug substances and products for use in animal feed. CVM will continue to use the current GRAS affirmation petition process.
Total	\$3,922	\$1,469	21		2	

Food and Drug Administration
National Center for Toxicological Research FY 2007 Strategic Redeployment
(in Thousands)

Program	FY2006 Enacted	Strategic Redeployment	Program Increases	FY2007
National Center for Toxicological Research	\$40,740	\$7,033	\$533	\$34,240

Program Areas	Redeployment Amount			FTE	Strategy
	BASE PROGRAM \$	AMOUNT REDEPLOYED \$	FTE BASE		
To fund FY 2007 priority initiatives such as Food Defense, Pandemic Preparedness, and Human Tissues Initiatives, FDA re-deployed resources from base programs.					
Infrastructure Support from NCTR program allocation					NCTR will focus on standards development and biomarker identification to improve the tools available for product review. NCTR will continue and expand energy saving measures. NCTR will use leveraged collaborative resources (National Institute for Environmental Health Sciences/National Institute for Child Health & Human Development/EPA) to maintain laboratory critical mass.
Systems Biology	\$7,588	\$6,222	0	0	NCTR will leverage intra-agency (OWH) and inter-agency research to continue safety assessments.
Genetic and Reproductive Toxicology	\$12,518	\$404	75.43	3	NCTR will continue to leverage research in safety assessment of FDA regulated compounds. NCTR will phase out studies on dietary modulation of risk in rodents.
Biohazard Identification	\$2,740	\$211	23.79	2	NCTR will continue to develop rapid methods to detect biological agents or foodborne contaminants. NCTR will leverage research in antimicrobial resistance.
Total	\$26,935	\$7,033	129	7	

**Food and Drug Administration
Office of Regulatory Affairs FY 2007 Strategic Redeployment
(In Thousands)**

Program Areas	Redeployment Amount			Strategy
	BASE PROGRAM \$	AMOUNT REDEPLOYED \$	FTE BASE	
Drug Product Surveillance - Domestic Drugs Program	\$5,050	\$498	44.3	For Meeting Public Health Commitment The redeployment of domestic sample analysis resources will not impact FDA's ability to protect the public health because ORA will target higher risk products by conducting selective sampling based upon product health hazard susceptibility and product threat level potential. We will continue to leverage with state governments via partnerships and contracts.
Drug Product Surveillance - Import Drugs Program			1.8	The redeployment of import sample analysis resources will not impact FDA's ability to protect the public health because ORA will target higher risk products by conducting selective sampling based on importer/country of origin, health hazard susceptibility, and threat level susceptibility of product.
Subtotal	\$8,071	\$277	70.8	
Field Animal Drugs and Feeds - Overall FY07 Strategic Redeployment	\$286,640	\$1,661	356	
NADA Pre-Approval Inspections Program and Bioresearch Monitoring Program			1.0	
Feed Manufacturing Program	\$2,109	\$210	18.5	The number of applications in this area never reached the level anticipated. Therefore, the 30 inspectional resources are being redirected without impact to public health protection.
Feed Contaminants Program	\$1,197	\$735	10.5	The redeployment of inspectional resources will not impact FDA's ability to protect the public health because ORA will target the highest risk medicated feed firms and products and will continue to leverage with state governments via partnerships and contracts in the feed manufacturing program area. ORA will not be reducing BSE coverage as a result of this redeployment.
Import Sample Analysis Program	\$2,348	\$63	20.6	The redeployment of domestic sample analysis resources will not impact FDA's ability to protect the public health because ORA will target higher risk products by conducting selective sampling based upon product health hazard susceptibility and product threat level potential. We will continue to leverage with state governments via partnerships and contracts in the feed contaminates program area.
Animal Drugs and Feed Research	\$5,221	\$210	45.8	The redeployment of import sample analysis resources will not impact FDA's ability to protect the public health because ORA will target higher risk products by conducting selective sampling based on importer/country of origin, health hazard susceptibility, and threat level susceptibility of product.
Subtotal	\$694	\$42	6	
	\$11,569	\$1,260	101	
Total FY07 Strategic Redeployment	\$421,543	\$11,442	1,504	48

*Please note that the references to "compliance and recall functions involving food, human drugs, and animal drugs and feeds" on pages 47 and 261 of the FY2007 Budget Request are erroneous. There will be no redeployment involving this program.

Food and Drug Administration
Other Activities FY 2007 Strategic Redeployment
(In Thousands)

Program	FY 2006 Enacted	Strategic Redeployment	Program Increases	FY2007
Other Activities	\$86,905	\$5,497	\$6,828	\$88,236

To fund FY 2007 priority initiatives such as activities such as Pandemic Preparedness, Food Defense, and Drug Safety, the Other Activities program will reduce the number of the FTE through attrition, selective replacement of vacant positions, and other workforce restructuring strategies.

Program Areas	Redeployment Amount		Strategy	
	BASE PROGRAM \$	REDEPLOYED \$	FTE BASE	FTE
Other Activities ¹	\$86,905	\$5,497	546	19
Total	\$86,905	\$5,497	546	19

Within the Other Activities account, we will continue efforts to consolidate programmatic functions and streamline operations to ensure that mission-critical functions continue effectively.

¹ The program will reduce the number of FTE through attrition, selective replacement of vacant positions, and other workforce restructuring strategies.

Senator VON ESCHENBACH. We have gone through the entire portfolio across the various centers and offices with the FDA, worked extensively with the staff within those offices to look for those opportunities and those efficiencies where we could leverage, synergize, and partner, and we will provide the detail for each of those particular parts of the portfolio for you.

PANDEMIC INFLUENZA

Senator BENNETT. All right. Thank you.

Last night, as I was watching television, which I don't often do—the news programs on television strike me as being more fictional than the sitcoms in many cases—running across the bottom of one of them was constant reference to Secretary Leavitt's warning with respect to pandemics.

And you discussed pandemic influenza preparedness at some length in your testimony, and we provided \$20 million for pandemic preparedness in fiscal 2006. Now you are asking for an additional \$30 million.

For those who do watch television and the streamer that runs across the bottom, could you discuss FDA's overall role in preparing for a pandemic and kind of tell us what you see in that whole area coming ahead for us?

Dr. VON ESCHENBACH. Thank you, Mr. Chairman.

I believe your question points out a very essential and critical element in our overall plan for a pandemic, and that particular element is the essential role that the FDA must play across a large portfolio of opportunity.

The role being to make certain that we are proactively helping to develop and to approve vaccines, antivirals and, devices that could be used for diagnostic purposes as well as devices that may have to be used ultimately with regard to human protection and support. And the important area that needs to be included in the portfolio, and that is the attention that needs to be paid to food animal.

In each of these areas, FDA plays and must continue to play a critically important role in that process. We are engaged, for example, in working proactively with companies in the industry to help stimulate the development of vaccines, to help them improve current vaccine production capabilities, including the utilization of cell-based techniques in addition to the traditional egg-based techniques that have been used.

Senator BENNETT. Let me interrupt you there quickly because I have been contacted by an American company that works on the issue of cell-based techniques as opposed to egg-based. And I want to call your attention to the fact that there are American companies that are in this field, and there has been concern raised about contracts being given overseas that are primarily to egg-based fixes, while there are American companies that complain that they are being overlooked.

And I would ask you to pay personal attention to that as we go forward because it has to do with volume.

Dr. VON ESCHENBACH. I certainly will continue to look into that, as will the rest of the agency, and pay very close attention to that. Because our commitment is to broaden the portfolio as widely as

possible to make as many opportunities and options available with regard to the development of new vaccines, specifically directed to H5N1.

With regard to antivirals, just as an example of the FDA's commitment, we are actively looking at opportunities to enhance shelf life of antivirals such as Tamiflu, which would significantly increase and enhance our abilities with regard to stockpile.

In devices, we work collaboratively with the CDC and recently approved in a very rapid period of time a diagnostic device, which can be used in processes of screening and looking for the first and earliest signs of H5N1.

And one of the areas I have pointed out which we needed to include into the FDA's commitment, and where a significant amount of the new funds are being directed, has to do with issues with regard to animal welfare, including the ability to regulate how animals will be used and making sure that we check and look for residue or traces of antivirals because we are concerned about the development of resistance in animals and humans.

But also should there be an outbreak or pandemic of avian flu within our bird population, the destruction of those food animals places the FDA in a critically important role with regard to regulating the processes of destruction and assuring that there is no contamination and risk for human health.

So it is a very broad portfolio, and we initiated after I arrived at FDA an integrated task force within FDA so that all these parts and pieces are now being coordinated and integrated into a cohesive effort so that FDA contributes appropriately to the larger initiative being carried out at the Department of Health and Human Services and in other agencies.

Senator BENNETT. Thank you very much. I would note that the company that contacted me is not located in Utah.

Senator Kohl.

Senator KOHL. Thank you, Mr. Chairman.

GENERIC DRUGS

Dr. von Eschenbach, the FDA plans to spend over \$400 million to approve approximately 88 new brand-name drugs and just \$65 million to approve over 400 new generic drugs in fiscal year 2007. There are currently over 800 generic drugs waiting to be reviewed at FDA, and the generics waiting list is expected to grow, as you know.

Now I understand the importance of reviewing and approving new drugs. They are often breakthroughs in the treatment of disease. However, according to the Congressional Budget Office, generic drugs on the market now save consumers an estimated \$8 billion to \$10 billion a year at retail pharmacies, and this doesn't include the money saved when they are used in hospitals.

As you know, they bring a big bang for the buck. And while the backlog continues to grow, your budget doesn't seem to make any effort to reduce that backlog. It seems that a relatively small increase, especially in relation to the money you spend to approve brand-name drugs, could make a big dent with respect to generics. How do you answer that?

Dr. VON ESCHENBACH. Thank you very much, Senator Kohl, for addressing what we believe is a very important and critical issue.

As you point out, we do want to continue to be sure that we are nurturing and supporting the innovative opportunities to continue to bring new solutions to patients, especially based on the progress that is being made in biomedical research and molecular medicine. At the same time, however, we are equally committed to being certain that we can provide access to patients to a wide portfolio of these drugs, including the availability of generics.

Over a period of time, we have a commitment to the generic program using all of the dollars that have been authorized for that purpose and have seen a continuous increase in the number of generics being approved each year. It is also true that the number of applications have also continued to increase.

We are attempting to address this problem in a variety of ways. First, we are giving priority to the first generic available. That is enabling us to assure that at least across the entire portfolio, Americans have access to one alternative to the innovator drug.

In fact, we believe that program has been successful, to the extent that we are approving first generics almost simultaneously with patent issues having been resolved. We have narrowed any gap between the legal barriers and the regulatory barriers making those drugs available to patients.

With regard to volume, we are at a point now where we are approving more than one generic drug on the average every day. Having said that, we also recognize the need for continuous improvement in the process, to continue to expand our ability to grow the portfolio to alleviate the backlog.

We are directing more people to the effort of the approval process. We are working with manufacturers to enhance the quality of their submissions in order to reduce cycle time to approval.

Most importantly, we are improving our own internal processes, especially by moving from paper-based regulatory approval processes to electronic based. And we believe this electronic infrastructure will be a significant step forward in enhancing the rapidity of our ability to process these applications and eliminate the backlog.

GENERIC DRUG BACKLOG

Senator KOHL. In spite of all of that, there are 800 generic drugs waiting to be reviewed and approved at the FDA, and that waiting list is expected to grow. So why don't we find a way, understanding how important these generic drugs are in helping people save money, why don't we find a way to more quickly address this backlog?

Do you see that as a high priority that you want to get at, or is it business as usual?

Dr. VON ESCHENBACH. No, sir.

Senator BENNETT. If I could just do the math? If they have 800, and they are doing one a day, and they don't work Saturdays and Sundays, that is about 3 years of backlog.

Senator KOHL. Thank you.

Dr. VON ESCHENBACH. Senator, let me approach the question in the following way. We are committed, as you are, to being able to expand the portfolio of access to various solutions for the American

people. And to do that, I believe really requires a process improvement. It is a way of looking at this entire continuum and looking for places in which we can improve cycle time, where we can improve the ability to move larger volumes of these applications more effectively through the system.

And as I indicated, the strategies that we are embarking upon are more people, more effective means of processing applications, including electronic submissions and electronic review, and working more collaboratively and proactively with the manufacturers of these generics in order for them to be able to enhance their applications and improve the application process.

We believe that by a multi-pronged effort, we will find incremental benefits along the entire process improvement continuum. The end result being more generic drugs coming, being made available to the American people.

Senator KOHL. Of course, you understand the American people want every generic drug that can be approved to be approved because it is an immediate tremendous saving in their pocket, right? And that is why we are here. That is a basic reason why we are here.

I just make that comment, and I turn it back to you, Mr. Chairman.

Senator BENNETT. Yes. I mean, a 3-year backlog, and you add in holidays, you get to 3.5.

Senator KOHL. Thank you again.

Dr. VON ESCHENBACH. Well, I think—

Senator BENNETT. That is more significant than I had realized.

Dr. VON ESCHENBACH. Well, I think one of the important things I would like to also emphasize—and apologize if I didn't make it as clear as I should have—is that in looking at the large volume of generics and what is available to the American people, we are looking at this in a hierarchical fashion.

First and foremost, we want to be sure that across the continuum of drugs that there is at least one generic available for any one of those particular drugs or solutions. Then there are follow-on generics after that or additional generics that are complementary or perhaps identical to that same generic.

Now the entire portfolio will always continue to grow, but there is a point where we believe that at least being sure that there are available drugs, generic drugs for every condition and in every situation and circumstance will be our first priority.

Senator BENNETT. So you are saying you are prioritizing them so that the generic that would benefit the greatest number of people will get moved up in the—

Dr. VON ESCHENBACH. Exactly, sir. In order to put the backlog into perspective, it would be one thing if we had a backlog in which there was an innovator drug for which there was no alternative generic. That would be a backlog that would have a critical impact on the health and welfare of the American people.

But if the backlog is one in which we already have three or four generics available for that particular drug, and there is a backlog of three or four other applications, that is going to get less priority in the hierarchical system.

Senator BENNETT. Well, I encourage you to continue to do that, and that is prudent management. But it would be helpful if the total number could come down and the total backlog could shrink a little.

CRITICAL PATH TO PERSONALIZED MEDICINE

Let me focus for a minute on your new initiative called the Critical Path to Personalized Medicine. That is an intriguing title, and this is obviously a long-term investment on your part.

Tell us what the ultimate goals are and how long you think it will take to achieve those goals. Or is this something that the goals will always be coming up, so this is a long-term program that will continue?

Dr. VON ESCHENBACH. Well, Mr. Chairman, I have benefitted greatly from my previous experience in being able to witness firsthand the tremendous progress that is being made in biomedical research and the literal explosion in our ability to understand diseases and even human health and nutrition from a genetic and molecular perspective.

And that discovery is really opening up for us the opportunity to develop new solutions, new products that are very different and unlike the products and solutions that we have seen in the past. We need a new bridge between that discovery to the delivery of those new solutions to patients, and that bridge of development is the bridge that the FDA is responsible for and is nurturing.

And it is the critical path from that discovery to that delivery that we are committed to by bringing to the regulatory process the science that has been involved in the discovery and the development of these new interventions and the science and technology that will be necessary in order to regulate and approve these new solutions and new products with regard to their safety and their efficacy.

So, in that context, with regard to that vision of what we are trying to accomplish, it will be an ongoing iterative process. We will continue to develop it as the science and technology continues to develop it.

But our goal is to make certain that these new solutions that we are experiencing by virtue of our investment in biomedical research at the NIH and in other areas will, in fact, translate into solutions that can and will be delivered rapidly, effectively, and safely to the American people.

Senator BENNETT. Well, one of the frustrations that I have had since I have been in the Senate is that almost none of the discussion about health care has anything to do with health. It is always focused on acute care or after the fact kind of care.

And if I hear correctly what you are saying, FDA is making a commitment for keeping people healthy prior to the time when they would need acute care and taking advantage of the science that is being developed at NIH and elsewhere.

And if we are successful and keep people healthy at the front end, we presumably save money at the back end. Is this a fair summary of what it is you are aiming for?

Dr. VON ESCHENBACH. It is an absolutely insightful summary, and I appreciate you framing it in that way. We believe that the

opportunities that are now available to us, the opportunities that the FDA can make possible for the American people, and for the rest of the world, by virtue of this critical path from discovery to delivery is the fact that medicine will be more preemptive or preventive.

We will have the tools to be able to understand the earliest stages in the development of many diseases and be able to then have products that will be able to be delivered to preempt that process. Being able to develop and regulate approval of those products will require a new FDA, the FDA of the 21st century.

And so, we will see cost benefits to that by moving out of a model that is predominantly focused on the treatment of established disease to a model in which we will have the solutions and tools to detect diseases much earlier in their development and then to be able to intervene and preempt them.

It will also be personalized. We are seeing increasingly opportunities to be able to define the right intervention for the right patient based on our understanding of these fundamental molecular mechanisms. And we are seeing new targeted drugs becoming available and coming to the FDA for regulatory approval.

If we get the right drug to the right patient, we eliminate the waste that occurs in the old system, the empiric system, where we are giving patients an intervention based on a statistical probability of success, but not knowing whether it will work in that patient or another patient. Just the fact that we can eliminate waste will have significant implications for our total expenditures in health care.

Senator BENNETT. I would like to pursue that with you in some detail because I think, ultimately, that is the only solution to our spiraling increase in Medicare and private health care costs.

Dr. VON ESCHENBACH. I would look forward to that, Senator.

Senator BENNETT. Yes. Senator Kohl.

GENERIC DRUGS

Senator KOHL. Thank you very much.

Just to add a final word on generics, you stated that you prioritized to be sure that we have at least a generic, if not two, available for every brand-name drug. I would like to ask my staff to work with your staff to satisfy me that, in fact, we are doing a good enough job in meeting at least that minimum kind of a condition which, as you point out, is very important, and I would agree.

Dr. VON ESCHENBACH. We would welcome that, Senator.

Senator KOHL. Thank you.

Dr. VON ESCHENBACH. And look forward to working with your staff.

AVIAN INFLUENZA

Senator KOHL. Dr. von Eschenbach, I was recently looking at some news reports on avian flu, and these two reports seemed to summarize, I think, what many people are feeling.

The first report quoted Dr. Gerberding of the CDC as saying that our current situation is not a good one. Secretary Johanns, on the other hand, was quoted that same day as stating that bird flu is coming to America, but he said that we are ready and "know how

to deal with it, and we will deal with it.” And just last week, he testified to us that, “We are well prepared for bird flu.”

It is understandable why many people are confused and uncertain and concerned about how to react. So from your perspective, are we prepared for a bird flu outbreak? How much vaccine do we have on hand now? And please talk about our ability to obtain or make more vaccine.

Dr. VON ESCHENBACH. Well, Senator—

Senator KOHL. Do you think we are well prepared?

Dr. VON ESCHENBACH. Pardon me, sir?

Senator KOHL. How would you summarize our situation with respect to the possibility of a bird flu outbreak?

Dr. VON ESCHENBACH. One of the things that I have appreciated is the fact that, as Secretary Leavitt has indicated, we are in a race. We are in a race with regard to our ability to mobilize and prepare all of the particular interventions and solutions that will be necessary to deal with an avian flu outbreak in humans.

And that race to prepare is in contrast to the race that the virus is engaged in with regard to its mutations. We don't know and can't predict exactly how long it may take for the virus to undergo the mutations that might be necessary for human-to-human transmission. We certainly have seen enough with regard to the virus to be alarmed and concerned that that ultimately might occur.

Having witnessed the mobilization that is occurring with regard to not only our own infrastructure within the United States, but around the world, I believe that we are engaged now in a very positive and very constructive and productive effort to bring all of the components to bear. As I indicated, the FDA is taking its role in a very integrated and comprehensive way to look across this continuum, to accelerate the ability to develop vaccines.

We cannot develop a vaccine for the human-to-human virus until that virus occurs, but we are developing vaccines for the H5N1 that has already occurred. And we are also developing seed strains so that we have in place variations of the virus so that we would be already prepared to move to the next step to mass production of vaccines once we got the right match.

So I use that as an example to point out that it is a problem that requires a comprehensive, integrated, collaborative solution. It is one in which we will look across the wide portfolio of interventions, and it will go beyond just vaccines to also include, as I have indicated before, antivirals, and diagnostic devices.

Senator KOHL. But just last week, the United Nations stated that bird flu could arrive in the United States between 6 and 12 months from now, which is imminent. So if these predictions are correct, the virus could arrive in the United States before we have the capability to make mass quantities of vaccines.

What advice do you have for people all across our country who are concerned about this imminence, this possibility within 6 to 12 months?

Dr. VON ESCHENBACH. Well, I think, as Secretary Leavitt has indicated, we need to be aware of the threat. We need to not panic, but we need to prepare in the sense of anticipating and being aware of the fact that this is a threat that could strike us.

It has not happened at this point in the sense of having the avian form of the disease in the United States, but that is expected to occur. It has not happened with regard to a strain that has human-to-human transmission capabilities.

But I think as far as the public is concerned, the continued support of the efforts that are being made across the public health continuum—not only in the Department of Health and Human Services, but throughout the rest of the academic world and in conjunctions with WHO—as you pointed out, I think it is a commitment to prepare and to prepare as rapidly as possible is the most important contribution we could make at this point.

Senator KOHL. Thank you, Mr. Chairman.

Senator BENNETT. Senator Harkin.

BOVINE SPONGIFORM ENCEPHALOPATHY

Senator HARKIN. Thank you very much, Mr. Chairman. And I apologize for being late. We had an authorizing committee hearing prior to this, not the appropriations.

But I thank you, Mr. Chairman, and welcome our witnesses here, especially Dr. von Eschenbach, whom I have worked with a great deal at NIH over the years.

I will get right to the point. Maybe this has been asked before, but I don't know if anything has been brought up about the recent case of BSE that was just discovered in Alabama.

Senator BENNETT. It hasn't been asked. So go ahead.

Senator HARKIN. Thanks, Mr. Chairman.

Well, as you know, it is in the press now that it was confirmed that we have another animal, a 10-year-old cow in Alabama tested positive for BSE, and now they are looking at the herd and the feed and everything else to try to figure out if there were other animals contaminated or where this contamination may have come from.

Now FDA recently proposed several changes to the feed ban rule that it first adopted in 1997. The main adjustment proposed is that brain and spinal cord from cattle would be banned from all animal feed, not just from cattle feed, okay? So far, so good.

However, the loophole that currently exists of allowing poultry litter—yes, you heard me right—poultry litter to be fed to cattle would continue.

So we have a situation where you can take some of the SRMs, specified risk material, from cattle, a ruminant animal, feed it to chicken. Some of that gets into the litter. The litter is then fed to a ruminant animal. The prions exist, and they may exist in the SRMs from the slaughtered, go into chicken feed, fall into the litter, and be fed back to a ruminant animal.

Canada is in the process of strengthening its feed ban rule to prohibit all, all specified risk materials from all animal feed, including pet food. That is, Canada is going beyond just the brain and spinal column. Canada has already banned poultry litter and plate waste from cattle feed.

Now FDA clearly acknowledges that the main cause of BSE in cattle is from contaminated feed. In fact, the feed rules are routinely cited by USDA and FDA officials as our first line of defense against BSE. But in this case, FDA, with these new proposed rules,

appears to be preparing to come out with a weaker feed rule than Canada, weaker than has been called for by experts on BSE.

In other words, it would still be permissible to feed cattle byproducts with a high risk of BSE back to cattle through poultry litter. Now, again, I don't know what the reasons for allowing that are, but I am just wondering with this proposed rule, FDA proposed rule, FDA will only prohibit a partial list of SRMs from all animal feed, a partial list.

In addition, FDA is not closing the loophole that currently exists by allowing poultry litter to be fed to cattle. This leaves a clear circle of transmission wide open, where the SRMs that are not prohibited by the proposed rule could be fed to poultry, and then the poultry litter fed back to cattle. How does the FDA justify not closing the poultry litter loophole?

Dr. VON ESCHENBACH. Senator, let me first begin by saying I appreciate the question and thank you for it because it is addressing an issue that, as you pointed out, with the recent awareness in the press of another cow being detected with BSE, it has raised concerns. And it is important that we address them.

The feed ban that was put in place in 1997 was done in a way to be able to ban high-risk materials and to be able to over a period of time, continue to monitor and inspect and be sure that processes were being appropriately applied. So FDA has been working closely with USDA. As it has been responsible for the issues with regard to cattle, FDA has been approaching the issues with regard to animal feed.

Throughout that period of time, and as you have pointed out, the processes that we put in place have, as we have gone through looked for compliance with regard to the processes, we have found in all the inspections over 99 percent compliance with the rules. And during that period of time, over 800,000—or at least at this point with regard to 650,000 high-risk animals that the FDA has identified, there have only been 2 cases of BSE, and those 2 cases have been in animals that were born before the feed ban was put in place.

Now I emphasize that because I think it is important to point out that the processes that have been in place since 1997 have had a high degree of compliance, and in fact, the risk of BSE in the cattle population at this point in time has only involved 2 animals, and both those animals were born before this ban was put in place.

Having said that, as you have pointed out, the FDA recently went a step further to further strengthen the feed ban rule and put in additional bans, as you have indicated.

Now with regard to the specifics of the transmission of BSE in prions in the droppings from poultry, if I could permit—with your permission—to have Steve Sundlof, the head of our Center for Veterinary Medicine, who is responsible for this area, he may be able to give you a much more precise scientific answer with regard to the risk of that particular aspect of possible transmission of BSE.

POULTRY LITTER AND BSE TRANSMISSION

Senator HARKIN. It is up to the Chairman.

Senator BENNETT. We could follow up.

Senator HARKIN. It is up to the Chairman. Yes, that is fine.

Senator BENNETT. Do you want to follow up quickly?

Senator HARKIN. If that would be okay with you, Mr. Chairman?

Senator BENNETT. Sure. Go ahead.

Mr. SUNDLOF. Thank you, Senator Harkin.

I am Steve Sundlof, the Director of the FDA Center for Veterinary Medicine, and it is my center that regulates the safety of all animal feeds, including pet foods.

To get to your precise question regarding poultry litter, first of all, we have evaluated the potential risk of poultry litter to spread BSE among cattle, and we find that to be very low for a number of reasons. First of all, the amount of animal protein in that poultry litter is very small. Secondly, it comprises a small part of the cattle diet. Thirdly, when we put it through some of our risk assessment models, it appears that that risk presently, as the rule is written, represents an extremely low risk.

By proposing that all brains and spinal cords from cattle over the age of 30 months be eliminated from all animal feeds, you have taken 90 percent of whatever remaining infectivity there exists out there, and you have taken that out of any poultry diet. So now with the new proposed rule, you have actually reduced any potential risk from poultry litter by another 90 percent.

And again, that is 90 percent of a very, very small risk to begin with. And so, the proposal really addresses a lot of the issues that remain around poultry litter.

Senator HARKIN. Is it possible, Mr. Sundlof, is it possible for the prions to come from a ruminant animal that actually might be fed to poultry or drop in the litter, and that litter could then possibly be fed back to a ruminant animal?

Mr. SUNDLOF. It is possible, but the amount that would be—first of all, if you take the brain and spinal cord out, you have eliminated 90 percent of whatever infectivity could go into that.

Senator HARKIN. I understand. I understand that.

Mr. SUNDLOF. But the amount of animal protein that is in the litter is very, very small. Now, you know, we don't say, we never can say that the risk is absolutely zero. And so, to answer your question, yes, it is possible. But the probability of that occurring is very, very remote.

Senator HARKIN. Well, now, Canada has already banned poultry litter, right, from being fed?

Mr. SUNDLOF. That is true.

Senator HARKIN. That is true in Europe, too?

Mr. SUNDLOF. Yes.

Senator HARKIN. It is true around the rest of the world as far as I know. And my question, I guess you just raised this question in my mind, if poultry litter is so low in protein, why are they feeding it?

Senator BENNETT. Yes, that was the question I have. If it is so small, what does poultry litter bring to the table?

Mr. SUNDLOF. Well, a little cattle physiology here. Cattle are able to convert non-protein materials like cellulose, in terms of grass, actually into protein. So a large part of cattle diet is made up of material that is very low in protein, but in the rumen of the cattle, the microorganisms actually make protein, which then the cattle digest.

So in terms of why Canada and Europe and other countries don't feed poultry litter has to do more with the demographics. In the South, especially in the southeastern United States, cattle are raised on open land. They are raised in areas where there is a lot of poultry production in addition to cattle production.

Poultry litter becomes an issue. The poultry industry has to get rid of this product somehow. They can either spread it onto the land and use it for fertilizer. But in general, there is more than can be disposed of by that method. It does have a fairly high nutritional value for cattle. It is something that, strangely enough, cattle seem to like to eat. And those conditions really don't occur in other parts of this country and especially in Canada and Europe.

Senator HARKIN. Well, again, since everyone else has banned it, it seems like we are always looking for ways to somehow get around banning the elements, all SRMs, not just the high risk, but all SRMS from getting back into ruminant feed. There are ways we can do that. Other countries have done it.

BSE RULE AND HARMONIZATION WITH CANADA

Now I am told, Mr. Chairman, I am told that some FDA people told my staff they were working with Canada to make its rules similar to the United States. In other words, FDA is working, hoping to see that Canada weakens its rule to match that of the United States. Is that so? Are we working to try to get Canada to weaken its rule?

Dr. VON ESCHENBACH. We are exploring harmonization efforts with Canada.

Senator HARKIN. Now what does that mean?

Dr. VON ESCHENBACH. Well, that means that we are exploring whether or not, you know, this is a proposal—

Senator HARKIN. Are we exploring to get to their level or get them to our level?

Dr. VON ESCHENBACH. Well, we are holding discussions where we are looking at their assumptions behind their risk models compared to our risk models. And if we find that their risk models are a better reflection than what we have developed, then we would be willing to adjust our rule.

But also we are just in the discussion phases now, where we are sitting down and examining the assumptions that went into each of our rules to determine whether or not those are valid in our particular countries, and there may be. And in the case with Canada, there may be some valid reasons why they should be different.

Senator HARKIN. Mr. Chairman, you have given me more than enough time. I do have some follow-up questions on the next round.

Senator BENNETT. Surely. We will have another round.

Dr. von Eschenbach—and thank you, sir, for your expertise. You told me more about chicken litter than I probably wanted to know.

MEDICAL DEVICE USER FEES

One of the things that I have been interested in since I have had this assignment in the Senate has been user fees and particularly medical device user fees. I found that FDA was delighted to have the extra money from the user fees, which were being paid some-

what reluctantly on the part of the users, but paid in an effort to increase the performance and lower the backlog of approvals.

And there was a period when FDA simply took the money and then took the appropriated money that would have gone into improving performance and spent it someplace else. And I have been a bit of a nag on that issue and got an agreement out of OMB that that sort of thing would stop, that the user fees would, in fact, be matched with appropriated funds, and the two would be coupled rather than one becoming the replacement for the other. It is only fair that that be the case.

Could you bring us up to date on where we are with performance out of MDUFMA? Now I have a copy of the answer that was given in the House with respect to this, and that is part of the transcript now of the House hearing. And I find that useful, but give you the opportunity to comment in general terms as to where we are with respect to greater performance in the medical device area and other areas where user fees are being paid in an effort to make sure that things move more rapidly.

Dr. VON ESCHENBACH. Well, Senator, as I have come to understand it and appreciate it, with regard to MDUFMA, or the medical devices user fees, that particular program has not had as long a history of experience and process improvement as has PDUFA with regard to the experience at FDA. And obviously, with medical devices, that introduces its own set of complexities with regard to the review process.

Having said that, as MDUFMA has been implemented at the FDA, in most cases, there has been a full compliance with regard to the targets or the milestones that were put in place. But at the same time, it is also true that it has not been the case uniformly across the entire board and, in fact, in looking at even where we have met those milestones, the incremental improvement in terms of really being able to significantly reduce cycle time and streamline and accelerate the time to market is not to the degree that even we would be happy with and comfortable with.

So we are looking at this from the point of view of process improvement. We are looking at it and working collaboratively and cooperatively with the industry in order to be able to continue to find ways to accelerate the process and make it more effective.

We think there are opportunities to work with the industry, for example, with the preparation of their applications in a way that will help us proactively and prospectively be able to do that by greater consultations. We have noticed with regard to PDUFA that that opportunity for consultations before the application process has proven to be something highly attractive and very positive with regard to their experience.

So we are looking at this. As you have pointed out, these dollars will be focused and targeted for a specific purpose, and that will remain so. And we will look to continue to improve the process.

Senator BENNETT. Thank you. I don't want user fees to become general taxes that just go into the general fund and then may or may not be producing the result for which people are paying extra.

Senator Kohl.

FIELD INSPECTORS

Senator KOHL. Thank you, Mr. Chairman.

Dr. von Eschenbach, looking at your budget, it states that your field force of inspectors is going to decrease by some 48 to 60 people. It also says in your budget in the very same section that the number of FDA-regulated imported products requiring inspection is increasing exponentially.

Some of the other examples of activities that won't be performed as often by these inspectors, as I said, the analysis of imported and also domestic samples of food, inspections of veterinary feed manufacturers, inspections of human drug manufacturers, compliance and recall functions, including food, drugs, and animal drugs and feeds.

How do you justify cutting field inspectors right now when the requirement for them seems to be going up and not down? Do you really believe that this is the best place for you to be trying to save money?

Dr. VON ESCHENBACH. What we are attempting to do, Senator, is to look at this again—as I have indicated in an answer to a previous question—as a process improvement issue. In looking at the total portfolio of activities and asking questions, where can we streamline? Where can we make this more efficient so that we are getting more outputs vis-a-vis the resources that we have to utilize to do that, including the human resources and the number of people that are involved?

We think that there are opportunities to continue to improve the process. By, for example, focusing on preapproval inspections, working with manufacturers, working with regard to good manufacturing practice requirements, we can improve some of the processes and opportunities with regard to a proactive approach.

We are targeting inspections to areas of high risk so that we are utilizing the workforce in a more efficient, more targeted way so that we are focusing on the areas where we see the highest concerns or the highest risks as opposed to simply disseminating those resources with less impact.

So it is a process improvement problem. Looking at modern technologies that will enable us to enhance the ability to utilize the inspection process is another way we think we can continuously get more outputs, meet our responsibilities, but do that in a way that is efficient in the use of the human resources that we have so that we are deploying those where we see areas of higher public health need.

DRUG SAFETY OVERSIGHT BOARD

Senator KOHL. All right. Dr. von Eschenbach, your budget talks about the creation last year of an independent Drug Safety Oversight Board to oversee the management of important drug safety issues.

A quote from Secretary Leavitt regarding this board says, "The public has spoken. They want more oversight and more openness. We will address their concerns by cultivating openness and enhanced independence." That is his quote.

And yet the FDA has received criticism because the board now has no public representatives, meets in private, and publishes only vague summaries regarding what is discussed in these meetings. So how do you respond to these criticisms?

The board may be independent, but is it really transparent when the only members are from the FDA and other Government agencies and reports are so vague?

Dr. VON ESCHENBACH. Senator, this is an important area, obviously, with regard to our commitment to drug safety. And the Drug Safety Oversight Board, as you point out, does go beyond FDA, and it does include other Federal employees from the National Institutes of Health and from the Veterans Administration.

That provides us a couple of opportunities. One, it does broaden the input. It does enhance the expertise that is involved in this oversight review, and it does take it outside the walls of the FDA so that it is subject to a larger and more, if you will, independent analysis and review by individuals who are not part of the agency and not part of the FDA internal process.

The very fact that they are Government employees, however, provides a great deal of efficiency in the terms of which this board is able to function. First of all, it enables us to avoid some of the potential problems and barriers in timeliness that would come from having to have to resolve conflict of interest issues or problems should this be outside of the Government.

It allows us to deal with confidential proprietary information within the confines and constraints of the committee so that we are looking at data and information that is much more sensitive and, therefore, has the potential to be much more important and insightful with regard to the safety issues.

So we believe that it is a balance and a balance between a process that is framed within the rules and regulations of FOIA, the rules and regulations with regard to conflict of interest, while at the same time, it is broadening the input beyond the FDA and assuring that we have the right expertise of individuals who will be able to improve the oversight of these drug safety issues.

OPENNESS OF DRUG SAFETY OVERSIGHT BOARD

Senator KOHL. Well, Secretary Leavitt said that he wants to see more openness, more independence, and that he would take steps to improve that. Now if you meet in private, if the members are not public representatives, and if the reports that emanate from your meetings are not specific, what kind of openness is that?

Dr. VON ESCHENBACH. Well, I think there can be a great deal of attention paid to the openness and transparency of the process and the rules and regulations that frame how an oversight is being conducted. But the issues with regard to what is occurring in the internal discussions dealing with proprietary information, that in itself needs to continue to be protected or we won't be able to get the right information that we need to analyze and assess.

So I think it is a balance, and it is an interplay between a process that is well defined, open, and, if you will, perhaps more precisely is transparent in terms of how it is being conducted with the rules that govern and frame how things are being done.

But then the discussions occur within the context of the confidentiality that is required in order to protect proprietary interests and information that is not appropriate to disclose in a public venue. And the committee has been vigilant and active in its effort. There have been five meetings in 2005 looking at 17 different products.

So it is active. It is engaged. It is an ongoing effort, and I think it is a process of balance between making sure that there is an additional layer of oversight, but one that is still being conducted within the constraints and confines of what the law and the regulatory process makes possible.

Senator KOHL. Thank you, Mr. Chairman.

Senator BENNETT. Senator Harkin.

BOVINE SPONGIFORM ENCEPHALOPATHY

Senator HARKIN. Thank you, Mr. Chairman. Just one last follow-up on the BSE.

I understand that FDA is going with the weaker rule because they are concerned about the costs of a stronger rule. Well, we can't ignore cost, but consider the cost that our country is bearing in lost export markets already because of that. Or consider the potential cost if consumers lose confidence in eating beef.

I mean, you can argue about science and risk, but some things just make common sense. I mean, how many people know that cattle are fed chicken litter? Now that is not just the straw and the bedding, that is fecal matter. They are eating chicken feces, okay? And they are eating a lot of stuff that could fall into that litter that could be parts from SRMs that are fed a lot to poultry, a lot.

And since other countries have banned it, I don't know why we are so reluctant to do that. Ask anybody even in this audience, how many, if you had a choice between hamburger from a cow that never ate fecal matter or one that did, what do you think you would get? It makes common sense.

And my big concern is that with this recent case of BSE, obviously, I have an interest in this because I represent a lot of cattle feeders. I represent cattle people, and they are concerned about the loss of confidence that may happen if more of these problems start popping up.

You may hear from the other side or some other side about this. But it seems to me that a big part of the problem that we have right now is that both FDA and USDA are telling the public that the feed rules are a firewall, a true safeguard. But now what I am hearing is you are saying that the feed rules are based on probabilities, 90 percent here, 90 percent there. You know, probabilities.

Well, so what we are hearing, the rhetoric and the facts don't match. And I am just, again, concerned that we don't move ahead more aggressively to prohibit all SRMs, not just the high risk, all SRMs from all animal feed, including poultry, and to eliminate, finally get over that hurdle of plate waste.

I can't believe we still permit plate waste in this country going into ruminant animals. Most other countries don't, but we still permit it. So, again, that is all I have to say on that.

FOOD AND NUTRITION FTE

A couple of other things, Dr. von Eschenbach. Is it true that in this budget that there are somewhere between 50 and 80 FTEs that will be taken away or transferred out of the food safety and nutrition area? Am I wrong in that?

Are there any at all in this budget, are there FTEs being cut in food and nutrition?

Dr. VON ESCHENBACH. With regard to the area of food and nutrition, Senator, we are looking at redeploying activities within that area and synergizing and partnering in order to be able to meet the necessary commitments that we have within the budget. But do that in a way that is more efficient and more effective.

We are looking at opportunities, for example, where mechanisms with regard to our management of personnel and opportunities for early buyout will enable us to reduce the cost of our workforce without necessarily reducing the number of FTEs. I would have to—

Senator HARKIN. Okay. Are there any in the budget? That is all I want to know. In this budget before us, is there a reduction in full-time equivalents in food and nutrition?

Dr. VON ESCHENBACH. I will have to give you for the record the specific—

Senator HARKIN. Okay. If you don't know, then if you could get back to us, I would sure appreciate it.

Dr. VON ESCHENBACH [continuing]. FTE reductions. But as I indicated to a prior question, I want to reassure the committee that whatever reductions and whatever redeployments are made in resources, we are doing that in a way that it has not compromised the commitment to public health and to safety.

Senator HARKIN. I appreciate that.

[The information follows:]

FOOD AND NUTRITION FTE

The strategic redeployment will be offsetting the requested increases in fiscal year 2007 for critical, high priority initiatives such as Pandemic Preparedness and Food Defense. This would be a change in FTE levels of -64 for Center for Food Safety and Applied Nutrition and -22 in Food related Field activities.

The redeployment of the FTE in Center for Food Safety and Applied Nutrition will be made from programs such as food additives and food contact substances, research, cosmetics, dietary supplements, outreach and regulatory activities. The redeployment of the Food related Field FTE will be made in areas such as the collection and analysis of domestic and import food samples and in the management, supervision, and coordination of personnel at multiple locations.

DIETARY HEALTH SUPPLEMENTS EDUCATION ACT

Good manufacturing practices. Senator Hatch, the other Senator from Utah, and I 12 years ago joined forces. We got a bill passed called DSHEA, the Dietary Supplement Health and Education Act.

At that time, we put a provision in the law that mandates that FDA is supposed to come with good manufacturing practices, GMPs we called them. About every 2 years since that, we have been told that FDA is going to come up with good manufacturing practices, going to come up with the regulations. This persisted in the 1990s. It has persisted since then.

Twelve years later, we still don't have good manufacturing practices regulations. The industry is crying out for this. The public needs it. It will tend to get some of the bad actors and those that might be out there out of the business. It will set up good standards. And here I am told again, "very soon."

Can you give us your personal assurance that you will work with OMB to get the GMPs published, and can you give us any definitive date?

Dr. VON ESCHENBACH. Thank you, Senator. And we are, along with you, committed to continuing to the full implementation of DSHEA and meeting the requirements that have been involved in that important law.

With regard to the dietary supplement GMP, as you have indicated, it is at OMB. The staff of CFSAN have been working directly with them with regard to addressing any particular issues with regard to that GMP being finally issued.

I will continue to commit to you and ensure you that FDA will do everything that is needed and required to work with OMB to bring that about as rapidly as possible. I understand that it is—

Senator HARKIN. It is frustrating.

Dr. VON ESCHENBACH [continuing]. Imminent. But—

Senator HARKIN. It is frustrating. Dr. Crawford, when he was before the help committee last year, said—he assured us that the GMPs for dietary supplements will be published in the Federal Register within months. Still hasn't happened.

Senator BENNETT. Depends on your definition of "months."

Senator HARKIN. Okay. Well, I suppose if you meant a lot of months, yes.

Dr. VON ESCHENBACH. I have looked into this, Senator, and I can tell you that it is in process and in progress. I am led to believe and understand that the issues are being and have been addressed.

Senator HARKIN. Can you give us any idea, can we see something happening here in the next 30, 60, 90 days? Anything at all that we can hold you accountable for?

Dr. VON ESCHENBACH. Please hold me accountable for working with the OMB in an effort to make this come forward as you have requested.

Senator HARKIN. I won't press the issue further.

I just have one last question. I will wait until my next round. Thank you.

Senator BENNETT. Thank you.

The experience of working with OMB is one that I have had, and it was an administration 30 years ago or longer, I guess. But I don't think OMB has changed that much, and it is very difficult many times.

And I have been in the position of being a witness where I know what I want to say, but OMB has told me what I can say. So I think Dr. von Eschenbach's commitment is probably the only one he can make under these circumstances.

UNIFIED FINANCIAL MANAGEMENT SYSTEM

Unified Financial Management System. This is a project initiated in 2001 to integrate several financial management systems across the department. I am assuming we are talking IT here, all right?

Dr. VON ESCHENBACH. Financial management, yes, sir.

Senator BENNETT. Everyone has experience with IT programs that start out with great hope and anticipation and then end up being over budget and behind time. Originally, FDA's share of the total project through fiscal 2007 was estimated at \$36.5 million. This subcommittee has provided more than \$50 million over the last 5 years, and your budget requests an additional \$1.2 million.

These are not large sums, but it is my understanding that annual costs for the system were supposed to level off and go down after fiscal 2005. This has not been the case. Since 2004, annual costs have gone up roughly 37 percent.

Can you give us any kind of light at the end of this tunnel as to where we are going and what kind of progress we have been making?

Dr. VON ESCHENBACH. I would be happy to, Senator, and I also, with your permission, will call Kathy Heuer, who is the head of our Office of Finance and Management, to provide additional details.

As I have understood and appreciated the process, FDA is contributing its appropriate share to the larger HHS effort with regard to the UFMS initiative, and it has, in fact, undergone an activation period of time with activation costs for contractor support, training, vendor support for new tools and licenses, and a need to continue to stabilize the process with regard to its utilization.

We are anticipating and expecting that those activation costs will come to an end through the year 2007 and into early 2008, which will bring us then into a level of cost reductions and cost savings, in fact, with regard to once we have implemented the system fully.

So that is my expectation and anticipation of the process and how it will unfold. Kathy, if you would add to that?

Ms. HEUER. Thank you, Senator.

UFMS will be the largest financial management system on the civilian side of the Federal Government when fully implemented. It is a way to consolidate financial management across Health and Human Services, allowing for better integration of information, comparability of information, and sounder management decisions based on easier access to data.

The cost increase you reflected in terms of 2005, 2005 is the year that we implemented UFMS. We went live in April 2005. The original budget projections did not include operations and maintenance projections. Those are about \$3 million per year.

We have a consolidated operations and maintenance structure with the department. So that is something that we have to pay in addition. Those were not part of the original estimates in terms of the budget.

The original estimate in terms of the budget was just the project development, and that is why there is that increase, as you mentioned, the 37 percent going up because that was not included. Originally, it was just development. But now the operations and maintenance is on top of that.

As Dr. von Eschenbach said, when UFMS is fully developed into 2008, then the development costs will be eliminated, and our ongoing costs will just be the operations and maintenance costs.

Senator BENNETT. Thank you. I wish you well.

Ms. HEUER. Thank you.

Senator BENNETT. Senator Kohl.
 Senator KOHL. Thank you, Mr. Chairman. I have finished my questioning. I will defer to Senator Harkin.
 Senator BENNETT. Senator Harkin.

STRATEGIC REDEPLOYMENT

Senator HARKIN. Mr. Chairman, just one last thing. And again, Dr. von Eschenbach, you are going to get back to us on these FTEs?

Dr. VON ESCHENBACH. Yes, sir.

Senator HARKIN. The question I asked, I had information that in the budget there is a cut in FTEs in food and nutrition?

Dr. VON ESCHENBACH. Senator, I am looking forward to presenting to the entire committee for the record a detailed explanation—

Senator HARKIN. Okay.

Dr. VON ESCHENBACH [continuing]. Of the redeployment strategy across all of the centers and offices within FDA. So that it will define what the programmatic shifts are in those programs, along with what the FTE changes will be. And we will give that to you not only with regard to CFSAN, but with regard to the entire portfolio so that you will have that with regard to answering your question.

GELATIN CAPSULES FOR DIETARY SUPPLEMENTS

Senator HARKIN. Okay. My last question has to do with U.S. companies that want to export dietary supplements with gelatin capsules to Europe are first required to obtain a health certificate from the Food and Drug Administration, required to do so by the European Union.

Now I wrote you a letter about this on February 28. I don't expect you to have replied. That is a short time ago. But I wrote you a letter about this on February 28.

Now as I understand it, the EU requires U.S. companies to get a health certificate from FDA's Center for Food Safety and Nutrition. But according to the exporters that have talked to me, the EU does not require these certificates for pharmaceutical companies that are using the same gelatin capsules to export pharmaceuticals. But if you have a dietary supplement, same gelatin capsule, they require the FDA to give a health certificate.

Well, I am told that the FDA does not issue such certificates. I don't know if that is so or not, but do you have any—I don't want to catch you flat-footed on this, but I am told that FDA does not issue them. So they are kind of caught.

The EU says they have got to have a health certificate, and yet FDA says they don't issue those. So—

Dr. VON ESCHENBACH. Senator, I cannot give you the specific details in answer to that question. I would be happy to do that for the record or have one of the FDA staff that would be responsible for that respond.

Senator HARKIN. Well, please have your staff, and you personally, take a look at the letter I wrote you on February 28. My staff will give you a copy here. I understand how those things go. But take a look at that because it is a big issue.

Because it is the same gelatin capsule that pharmaceutical companies use. They order them from the same place, but the EU has rules that say you can't without a health certificate.

So, they are sort of caught in a bind here. I need to find out about that and what we can do to help them overcome this trade barrier.

Dr. VON ESCHENBACH. I will look into that for you, Senator.

Senator HARKIN. I appreciate that very much.

Thank you, Mr. Chairman.

[The information follows:]

HEALTH CERTIFICATES FOR GELATIN CAPSULES

FDA issues a certificate, sometimes called a health certificate, for bulk gelatin for human consumption exported to the European Union, also known as EU. In the certificate, FDA certifies compliance with relevant U.S. standards, which have been recognized for this purpose as equivalent to EU requirements for foods including dietary supplements. The EU requires the certificate include affirmations from the manufacturer and periodic state inspections confirming the gelatin is produced in accordance with U.S. standards, the gelatin meets certain criteria, and that raw materials are appropriately sourced.

The EU legislation separates requirements for foods and requirements for pharmaceuticals. However, to date it is only the United Kingdom, in its implementation of EU legislation, has stopped shipment of gelatin capsules containing dietary supplements. It is our understanding that our EU counterparts are trying to resolve the situation since the gelatin used in human food is, in most cases, identical to the gelatin used for pharmaceuticals.

ADDITIONAL COMMITTEE QUESTIONS

Senator BENNETT. Thank you.

Dr. von Eschenbach, we appreciate your attention to all of these questions and you and your staff's response to what our concerns are.

Dr. VON ESCHENBACH. Thank you, Mr. Chairman. And may I express to you and to the committee our gratitude, as I indicated at the very beginning, for your support.

I would also like to express personally, for however long I have the privilege to serve in this role, that both myself and the staff of the leadership of the FDA would look forward to an ongoing conversation and relationship about many of the important issues that you raise. Not simply at a time, for example, when we are requesting a budget appropriation, but in an ongoing basis.

We intend to be responsive and timely to requests that are provided to us by mail, but I look forward to that opportunity in person as well. And I know that that is reflected by the talented and wonderful people who are sitting behind me, who are the content experts that are at your disposal.

Thank you, sir.

[The following questions were not asked at the hearing, but were submitted to the Department for response subsequent to the hearing:]

QUESTIONS SUBMITTED BY SENATOR ROBERT F. BENNETT

MEDICAL DEVICE USER FEE AND MODERNIZATION ACT (MDUFMA)

Question. Please provide, for the record, specific information regarding FDA performance in each of the medical device user fee goal areas.

Answer. Secretary Thompson's November 2002 letter to Congress, also known as the FDA commitment letter, defines the performance objectives FDA is pursuing

under the Medical Device User Fee Act, or MDUFMA. The commitment letter defines a comprehensive set of challenging goals and a schedule for meeting the goals.

To allow FDA time to build its capacity to meet the ultimate goals set by MDUFMA for fiscal year 2007, the commitment letter provides for a phased implementation of goals, with the addition of more goals and higher performance expectations each year. In fiscal year 2005, 18 additional goals went into effect, with two exclusively for the Center for Biologics, Evaluation and Research, also known as CBER. Six additional goals go into effect in fiscal year 2006. In fiscal year 2007, FDA will be responsible for a total of 77 quantitative goals covering five receipt cohorts. FDA is expected to pursue eight additional nonquantifiable commitments, such as developing an appropriate bundling policy, continuing our efforts to develop mechanisms for the electronic receipt and review of applications, and improving the scheduling and timeliness of preapproval inspections.

Although we do not expect to meet every goal specified by MDUFMA, the trends are promising. Since some goals involve so few applications that missing the review time frame for a single application by a single day can result in "failure" to meet a MDUFMA goal. We are, in general, showing better performance as we implement new policies and procedures designed to improve the timeliness of our review processes. Although it is too soon to know what our final performance statistics will show, since many goals still have applications that remain open, our performance on applications within more recent receipt cohorts is better than our performance within older cohorts. If you had taken a snapshot of performance for the fiscal year 2003, fiscal year 2004, and fiscal year 2005 receipt cohorts on December 31, 2005, you would see that FDA is meeting or exceeding 19 of the 24 goals in effect, and is not meeting only two goals. No applications have qualified for the remaining three goals.

We are confident that MDUFMA is producing positive results for FDA, for industry, and—of critical and highest importance—for patients and health care professionals.

I would be happy to provide FDA's performance report for fiscal year 2004 for the record. We will forward our fiscal year 2005 report when it is complete.

[The information follows:]



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

December 16, 2004

TO: The Secretary
Through: DS _____
COS _____
ES _____

FROM: The Acting Commissioner of Food and Drugs

SUBJECT: Annual Performance Report to Congress Required by the Medical Device User Fee and Modernization Act (MDUFMA)

BACKGROUND

Attached for your consideration is the annual performance report to Congress required by MDUFMA. MDUFMA amends the Federal Food, Drug, and Cosmetic Act to authorize FDA to collect user fees from manufacturers who submit certain applications to market medical devices. In exchange for this authority, MDUFMA requires that FDA pursue a comprehensive set of review performance goals and commitments to improve the timeliness and predictability of medical device reviews. MDUFMA's review performance goals were developed in recognition of the fact that FDA needs a 2-year start-up period (FY 2003 through FY 2004) to hire and train new staff and construct review program infrastructures before substantial progress in improving overall review performance is possible.

HIGHLIGHTS

Among the key achievements during FY 2004 were:

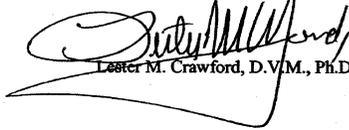
- **Guidance and Procedural Development.** FDA issued 11 MDUFMA guidance documents during FY 2004: 2 draft guidance documents, 7 final guidance documents, and 2 revised editions of final guidance documents that had been issued during FY 2003.
- **Stakeholder Communication and Consultation.** FDA expanded its outreach to stakeholders, providing additional information through the MDUFMA internet site (www.fda.gov/cdrh/mdufma), through presentations at industry and professional meetings, and at quarterly meetings with stakeholders. In December 2003, FDA held its first Annual Stakeholder Meeting to report on the implementation of MDUFMA and to hear directly from stakeholders.

Page 2 – The Secretary

- **Public Notification.** FDA published 27 *Federal Register* notices to provide essential information to stakeholders on new guidance documents, proposed rules, regulatory actions, user fees, and other topics, and to also request comments and suggestions from stakeholders.
- **Congressional Reporting.** FDA submitted its first MDUFMA performance report and first MDUFMA financial report to Congress covering FY 2003. FDA's new Office of Combination Products submitted its first annual report to Congress, which included information on MDUFMA-related products.
- **Hiring and Training of Staff.** The Center for Devices and Radiological Health applied 735 full-time equivalents (FTEs) to the process of reviewing device applications during FY 2004, an increase of 60 FTEs over FY 2002. The Center for Biologics Evaluation and Research applied 67 FTEs, an increase of 9 FTEs. FDA's hiring focused on priorities identified by product review groups. In addition, FDA expanded its use of outside experts.

RECOMMENDATION

I recommend that you review and approve the report and forward it to Congress.



Lester M. Crawford, D.V.M., Ph.D.

Attachments (2)
Tab A – Transmittal Letters
Tab B – Report to Congress

Trac #04 6398
Letters/Memo Drafted:D Delman:HF-40:11/17/04
Cleared: W Osborne, 11/18/04

Doc name: G:\wp\danad\MDUFMA Perf 04 ltrs, memo.doc



THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

MAR 28 2005

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The Honorable Richard Cheney
President
United States Senate
Washington, D.C. 20510

Dear Mr. President:

Enclosed for your consideration is the FY 2004 Performance Report to Congress required by the Medical Device User Fee and Modernization Act (MDUFMA), signed into law on October 26, 2002. MDUFMA amends the Federal Food, Drug, and Cosmetic Act to authorize the Food and Drug Administration to collect user fees from manufacturers who submit certain applications to market medical devices. In exchange for this authority, MDUFMA requires that FDA pursue a comprehensive set of review performance goals and commitments to improve the timeliness and predictability of medical device reviews.

In FY 2004, FDA continued to focus on consulting with its stakeholders through the MDUFMA Internet site (www.fda.gov/cdrh/mdufma), through presentations at industry and professional meetings, and at quarterly meetings; developing guidance documents; designing and building new review processes and improvements necessary to meet MDUFMA's challenging performance goals; publishing 27 Federal Register notices to provide essential information to stakeholders; and hiring and training new staff.

I hope you will find this report informative.

Sincerely,

Handwritten signature of Michael O. Leavitt in black ink.
Michael O. Leavitt

Enclosure



THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

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MAR 28 2005

The Honorable J. Dennis Hastert
Speaker of the House
Washington, D.C. 20515

Dear Mr. Speaker:

Enclosed for your consideration is the FY 2004 Performance Report to Congress required by the Medical Device User Fee and Modernization Act (MDUFMA), signed into law on October 26, 2002. MDUFMA amends the Federal Food, Drug, and Cosmetic Act to authorize the Food and Drug Administration to collect user fees from manufacturers who submit certain applications to market medical devices. In exchange for this authority, MDUFMA requires that FDA pursue a comprehensive set of review performance goals and commitments to improve the timeliness and predictability of medical device reviews.

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I hope you will find this report informative.

Sincerely,

A handwritten signature in black ink that reads "Michael O. Leavitt".

Michael O. Leavitt

Enclosure



THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

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MAR 28 2005

The Honorable Joe Barton
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

Enclosed for your consideration is the FY 2004 Performance Report to Congress required by the Medical Device User Fee and Modernization Act (MDUFMA), signed into law on October 26, 2002. MDUFMA amends the Federal Food, Drug, and Cosmetic Act to authorize the Food and Drug Administration to collect user fees from manufacturers who submit certain applications to market medical devices. In exchange for this authority, MDUFMA requires that FDA pursue a comprehensive set of review performance goals and commitments to improve the timeliness and predictability of medical device reviews.

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Sincerely,

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Michael O. Leavitt

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THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

MAR 28 2005

The Honorable John Dingell
Ranking Minority Member
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515

Dear Mr. Dingell:

Enclosed for your consideration is the FY 2004 Performance Report to Congress required by the Medical Device User Fee and Modernization Act (MDUFMA), signed into law on October 26, 2002. MDUFMA amends the Federal Food, Drug, and Cosmetic Act to authorize the Food and Drug Administration to collect user fees from manufacturers who submit certain applications to market medical devices. In exchange for this authority, MDUFMA requires that FDA pursue a comprehensive set of review performance goals and commitments to improve the timeliness and predictability of medical device reviews.

In FY 2004, FDA continued to focus on consulting with its stakeholders through the MDUFMA Internet site (www.fda.gov/cdrh/mdufma), through presentations at industry and professional meetings, and at quarterly meetings; developing guidance documents; designing and building new review processes and improvements necessary to meet MDUFMA's challenging performance goals; publishing 27 Federal Register notices to provide essential information to stakeholders; and hiring and training new staff.

I hope you will find this report informative.

Sincerely,

A handwritten signature in black ink that reads "Michael O. Leavitt".

Michael O. Leavitt

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THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

MAR 28 2005

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The Honorable Edward M. Kennedy
Ranking Minority Member
Committee on Health, Education, Labor and Pensions
United States Senate
Washington, D.C. 20510

Dear Senator Kennedy:

Enclosed for your consideration is the FY 2004 Performance Report to Congress required by the Medical Device User Fee and Modernization Act (MDUFMA), signed into law on October 26, 2002. MDUFMA amends the Federal Food, Drug, and Cosmetic Act to authorize the Food and Drug Administration to collect user fees from manufacturers who submit certain applications to market medical devices. In exchange for this authority, MDUFMA requires that FDA pursue a comprehensive set of review performance goals and commitments to improve the timeliness and predictability of medical device reviews.

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I hope you will find this report informative.

Sincerely,

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Michael O. Leavitt

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THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

MAR 28 2005

The Honorable Michael B. Enzi
Chairman
Committee on Health, Education, Labor and Pensions
United States Senate
Washington, D.C. 20510

Dear Senator Enzi:

Enclosed for your consideration is the FY 2004 Performance Report to Congress required by the Medical Device User Fee and Modernization Act (MDUFMA), signed into law on October 26, 2002. MDUFMA amends the Federal Food, Drug, and Cosmetic Act to authorize the Food and Drug Administration to collect user fees from manufacturers who submit certain applications to market medical devices. In exchange for this authority, MDUFMA requires that FDA pursue a comprehensive set of review performance goals and commitments to improve the timeliness and predictability of medical device reviews.

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Michael O. Leavitt

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Food and Drug Administration
Department of Health and Human Services

FY 2004 PERFORMANCE REPORT TO THE CONGRESS

for the

Medical Device User Fee and Modernization Act



Commissioner's Report

I am pleased to report that the Food and Drug Administration (FDA) is making good progress in implementing the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) and that the Agency's overall performance to date is consistent with the comprehensive and challenging performance goals that are a key feature of MDUFMA.

MDUFMA requires close collaboration with stakeholders and increased communication with applicants. FDA is working to clarify its regulatory requirements and make its decisions more transparent through new guidance and educational materials. We continue to make every effort to reduce the costs as well as the burden associated with product review. These efforts should help applicants improve the quality of their submissions, and will help FDA provide more rapid, better-focused reviews. Our ultimate objective is to make important new medical devices available to patients and health care providers earlier, while continuing to ensure the adequate safety and effectiveness of those devices.

FDA's efforts in fiscal year (FY) 2003 and FY 2004 provide a solid foundation to build on during FY 2005 and in future years.



Lester M. Crawford, D.V.M., Ph.D.
Acting Commissioner of Food and Drugs

Executive Summary

On October 26, 2002, MDUFMA was signed into law. MDUFMA amends the Federal Food, Drug, and Cosmetic Act (FD&C Act) to authorize FDA to collect user fees from manufacturers who submit certain applications to market medical devices. In exchange for this authority, MDUFMA requires that the FDA pursue a comprehensive set of review performance goals and commitments to improve the timeliness and predictability of medical device reviews.

FDA has made good progress in implementing MDUFMA and is making satisfactory progress towards achieving the performance goals set under MDUFMA. FDA has worked hard to communicate the new requirements and challenges of MDUFMA to its stakeholders. The Agency has worked with its stakeholders to ensure that the implementation of the new law proceeds smoothly. FDA is confident that the implementation of MDUFMA will result in significant benefits to industry, health care professionals, and, most importantly, patients.

FY 2004 Activities

FDA continued to focus on consulting with its stakeholders, developing guidance documents, and designing and building the new review processes and process improvements required to meet MDUFMA's challenging performance goals. As with FY 2003, only two quantifiable performance goals were in effect during FY 2004. Among the key achievements during FY 2004 were:

- **Guidance and Procedural Development.** FDA issued 11 MDUFMA guidance documents during FY 2004: two draft guidance documents, seven final guidance documents, and two revised editions of final guidance documents issued during FY 2003.
- **Stakeholder Communication and Consultation.** FDA expanded its outreach to stakeholders, providing additional information through the MDUFMA Internet site (www.fda.gov/cdrh/mdufma), through presentations at industry and professional meetings, and at quarterly meetings with stakeholders. In December 2003, FDA held its first Annual Stakeholder Meeting to report on the implementation of MDUFMA and to hear directly from stakeholders.
- **Public Notification.** FDA published 27 Federal Register notices to provide essential information to stakeholders on new guidance documents, proposed rules, regulatory actions, user fees, and other topics, and to also request comments and suggestions from stakeholders.
- **Congressional Reporting.** FDA submitted its first MDUFMA performance report and first MDUFMA financial report to Congress covering FY 2003. FDA's new Office of Combination Products submitted its first annual report to Congress, which included information on MDUFMA-related products.

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- **Hiring and Training of Staff.** The Center for Devices and Radiological Health (CDRH) applied 735 full-time equivalents (FTEs) to the process of reviewing device applications during FY 2004, an increase of 60 FTEs since FY 2002. The Center for Biologics Evaluation and Research (CBER) applied 67 FTEs, an increase of 9 FTEs. FDA's hiring focused on priorities identified by product review groups. In addition, FDA expanded its use of outside experts.

FY 2003 and FY 2004 Performance Goals

MDUFMA's review performance goals were developed in recognition of the fact that FDA needs a 2-year start-up period (FY 2003 through FY 2004) to hire and train new staff and construct review program infrastructures before substantial progress in improving overall review performance is possible. Consequently, most review performance goals do not go into effect until FY 2005. As of September 30, 2004, three submissions have been subject to specific MDUFMA performance goals and all were associated with FY 2003 submissions. FDA met the review time goal in two of the three submissions acted on in FY 2004. No FY 2004 amendments were received as of September 30, 2004.

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Introduction

... prompt approval and clearance of safe and effective devices is critical to the improvement of the public health so that patients may enjoy the benefits of devices to diagnose, treat, and prevent disease ...

— Section 101(1) of the Medical Device User Fee and Modernization Act of 2002.

On October 26, 2002, MDUFMA was signed into law. MDUFMA amends the FD&C Act to authorize FDA to collect fees from companies who submit certain applications for marketing of medical devices. In return, MDUFMA requires FDA to pursue a comprehensive set of device review performance goals that will significantly improve the timeliness and predictability of FDA's review of new devices.¹ These performance goals were developed collaboratively and are defined in the Department of Health and Human Services (DHHS) Secretary Thompson's November 14, 2002, letter to Congress.² Information about MDUFMA, including the text of the amendments and the performance goals and procedures, can be found at <http://www.fda.gov/oc/mdufma>.

MDUFMA requires the Secretary to submit two annual reports to Congress for each fiscal year fees are collected: 1) a performance report due within 60 days of the end of the fiscal year, and 2) a financial report due within 120 days of the end of the fiscal year. This document fulfills the first of these requirements for FY 2004. FDA's authority to collect user fees under MDUFMA expires after 5 years.

On April 1, 2004, MDUFMA was amended and expanded by the Medical Device Technical Corrections Act (MDTCA), P.L. 108-214. MDTCA amends MDUFMA to clarify Congress's intent and to improve and expand upon some features of MDUFMA. These changes did not affect the performance goals FDA is pursuing under MDUFMA.

¹ Section 738(g) of FD&C Act, as amended by MDUFMA. Except where noted, all statutory citations in this report are to the FD&C Act, as amended by MDUFMA.

² DHHS Secretary Thompson submitted the required letter to Congress on November 14, 2002 (Congressional Record, November 19, 2002, p. S11549). For convenience, this report refers to this letter as "FDA's Commitment Letter." The complete text of the letter is provided in Appendix A.

Overview of MDUFMA

Background

MDUFMA was signed into law on October 26, 2002, amending the FD&C Act to provide FDA important new responsibilities, resources, and challenges. The goal of MDUFMA is to better serve the public health by providing additional funds to FDA for "the process for the review of devices and the assurance of device safety and effectiveness so that statutorily mandated deadlines may be met." The user fees provided by MDUFMA, and the additional appropriations that go with the new law, will provide the following significant benefits:

- Safe and effective medical devices will reach patients more rapidly.
- Manufacturers will receive timely, high quality reviews with greater consistency.
- Resources will be provided to ensure that devices marketed in the United States continue to meet high standards for safety and effectiveness.

The majority of devices associated with MDUFMA are reviewed by CDRH. However, a number of devices that are critical to ensuring the safety, purity, and potency of biologic products, including assuring the safety of our nation's supply of blood and human tissue products, are reviewed by CBER. Additionally, CBER regulates diagnostic tests for retroviruses, including HIV, as well as devices used in cell and gene therapies. An Intercenter Agreement between CBER and CDRH discusses the types of devices regulated by CBER.

MDUFMA Commitments: Goals and Approaches

This report is concerned primarily with the performance goals that are an integral part of MDUFMA. FDA has prepared a summary of MDUFMA, including information on topics not covered by this report; see www.fda.gov/cdrh/mdufma/mdufmasummary.pdf. FDA also prepares an annual financial report that provides information on review fee revenues and expenses and compliance with MDUFMA requirements concerning the collection and use of those fees; the current and past reports are available at www.fda.gov/cdrh/mdufma/reports.

The MDUFMA has three particularly significant provisions related to FDA performance:

- User fees for premarket reviews, including Premarket Applications (PMAs), Product Development Protocols (PDPs), Biologics Licensing Applications (BLAs), certain supplements, and 510(k)s (premarket notification submissions). The revenues from these fees, and from additional appropriations for infrastructure, will allow FDA to pursue a set of performance goals that will provide patients earlier access to safe and effective technology, and will provide more interactive and rapid review to the medical device industry. A small business (sales and receipts of \$30 million or less) may pay a reduced fee. The

payment of a premarket review fee is not related to FDA's final decision on a submission.

- Establishment inspections may be conducted by accredited persons (third parties), under carefully prescribed conditions.
- New regulatory requirements for reprocessed single-use devices, including provisions requiring the submission of additional data on devices now being reprocessed, and a new category of premarket submission, the premarket report.

MDUFMA makes several other significant changes, including:

- The existing third-party 510(k) review program is continued through FY 2006.
- The review of combination products (products that combine elements of devices, drugs, or biologics) will be coordinated by a new office (the Office of Combination Products) in the Office of the Commissioner.
- FDA may require electronic registration of device establishments, when feasible.
- Manufacturers may provide electronic labeling for prescription devices used in health care facilities or by a health care professional.
- The sunset provision, which addresses how FDA is to determine the intended use of a device, is revoked.³ The effect is to make the requirement permanent.
- The law now explicitly provides for modular review of PMAs.

Phased-In Performance Goals

Performance goals increase in number, complexity, and difficulty beginning in FY 2005. Few objectively-measurable goals were applied during FY 2003 and FY 2004, allowing FDA time to hire staff, build infrastructure, provide guidance to industry, and take other actions to implement the new law. More goals go into effect each year from FY 2005 through FY 2007, and the goals become more demanding each year. For example, PMA "first action" goals can be met for the FY 2005 cohort if *75 percent* of the actions occur within the specified review time standard, but these goals require *80 percent* of actions to meet the standard for FY 2006, and *90 percent* for FY 2007. FDA must continually improve its processes and performance if it is to meet these objectives.

³ Applicable to section 513(i)(1)(E).

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MDUFMA's Performance Goals Are Phased In Through FY 2007					
Goal Type	FY 03	FY 04	FY 05	FY 06	FY 07
Measurable Goals Section I, Paragraphs A through H of the FDA Commitment Letter	2	2	20	26	27
Additional Commitments Section I, Paragraphs I through P of the FDA Commitment Letter	8	8	8	8	8
Total Goals and Commitments	10	10	28	34	35

Appendix C provides a table that summarizes all of MDUFMA's objectively-measurable performance goals in effect during each year through FY 2007.

MDUFMA Implementation

In addition to authorizing the FDA to collect user fees for medical device applications, MDUFMA established review performance goals for the Agency. These goals aim to improve review times for medical device applications by up to 25 percent in five years (even more improvement is expected for breakthrough devices). FDA's medical device program resources have been reduced in recent years, and there have been indications that review performance had begun to decline. MDUFMA's review performance goals recognize that FDA will need a two-year start-up period (FY 2003 through FY 2004) to hire and train new staff and rebuild review program infrastructures before it will be possible to make substantial progress in improving overall review performance. Consequently, most review performance goals do not go into effect until FY 2005. User fees, coupled with additional appropriations from Congress, will help the FDA more efficiently and more quickly make safe and effective medical devices available to the public.

FY 2004 Activities and Accomplishments

FDA continued to make steady progress in implementing MDUFMA in FY 2004 and is laying a sound foundation to enable it to vigorously pursue the ambitious performance goals defined under MDUFMA. However, there was no opportunity for FDA to apply either of the two review performance goals for FY 2004 (both related to FDA action on an amendment containing a complete response to an "approvable" letter).⁴ As a part of FDA's ongoing commitment to MDUFMA, the Agency is preparing, through guidance and procedural development, management initiatives, and outreach/education activities, to meet the more ambitious performance goals of FY 2005 through FY 2007. Highlights of the activities and accomplishments important to MDUFMA implementation are presented below.

- **Guidance and Procedural Development.** During FY 2004, FDA developed and published 11 guidance documents to explain FDA's requirements under MDUFMA and help applicants improve the quality of their applications.
- **Communications and Consultation with Stakeholders.** FDA expanded its outreach to stakeholders, providing additional information through the MDUFMA Internet site (www.fda.gov/cdrh/mdufma), FDA presentations at industry and professional meetings, and quarterly meetings with stakeholders.

⁴ FDA could not apply these goals because the specified conditions for these two goals did not occur before FY 2004 ended. That is, there was no instance where: 1) an applicant submitted an application during FY 2004; 2) FDA issued an "approvable" letter for that application; 3) the applicant submitted an amendment containing a complete response to FDA's "approvable" letter; 4) 30 days passed for FDA to take action on the amendment; and 5) the 30-day period for FDA action closed before the end of FY 2004. FDA often makes a decision on a PMA without issuing an "approvable" letter.

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- **First Annual Stakeholder Meeting.** FDA convened the first Annual MDUFMA Stakeholder Meeting on December 3, 2003, to report on the implementation of MDUFMA and to hear directly from stakeholders. The meeting included panel discussions of the user fee process, MDUFMA performance goals, bundling, modular PMA reviews, and other topics. FDA is using this information to refine the implementation of MDUFMA.
- **Reports to Congress.** FDA submitted the following first annual reports to Congress to keep them informed of the Agency's progress in implementing MDUFMA and to fulfill its obligations under the law.
 - FY 2003 MDUFMA Performance Report.
 - FY 2003 Financial Report on MDUFMA user fee receipts and expenditures.
 - Operations Report from FDA's Office of Combination Products.

Implementation Plans for FY 2005

During FY 2005, FDA will expand its efforts, through employee hiring, training, guidance development, electronic tracking/review system expansion, and outreach, to improve the timeliness and efficiency of device review programs and build FDA's capacity to meet the more challenging goals set for later years. Among the key MDUFMA activities scheduled for FY 2005 are:

- Eighteen more performance goals go into effect for FY 2005. As a result, more submissions will be subject to measurable performance goals, and FDA will have to sustain and improve its performance in order to achieve the higher level of performance expected for FY 2005.
- The modular review program, currently restricted to premarket applications, will be extended to panel-track PMA supplements, and FDA will work with stakeholders to develop performance goals for modular reviews.
- FDA will issue guidance explaining how pre-approval inspections may be completed in considerably less time.
- FDA will provide more substantive guidance on how third-party inspections are to be conducted. Additional guidance documents will be prepared; information on these and other efforts will be available on FDA's MDUFMA Internet site, www.fda.gov/cdrh/mdufma.

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Report on FY 2004 MDUFMA Performance

This report presents the Agency's performance on MDUFMA performance goals and commitments in FY 2004. Additionally, performance information originally presented in FDA's FY 2003 MDUFMA Performance Report has been updated to include additional actions the Agency has taken since its last report. Unless otherwise noted, all performance data in this section are as of September 30, 2004.

Performance Goals. MDUFMA requires that FDA meet specific performance goals. For each type of submission for which a medical device user fee is assessed, MDUFMA contains two types of performance goals:

- **Cycle Goals.** A cycle goal is a goal on a specified action that precedes a final action on the submission.
 For example, "First action major deficiency letters will issue within 120 days." A major deficiency letter is not a final action; the applicant can continue the review by preparing and submitting an amendment that addresses the deficiencies identified in FDA's letter.
- **Decision Goals.** A decision goal, on the other hand, is a goal on a final action, ending the review process.
 For example, "90 percent of submissions received in FY 2007 will have an FDA decision in 300 days."

Submissions received since the start of FY 2003 (October 1, 2002) are subject to MDUFMA's performance goals. FDA will report annually on the current fiscal year and will update performance from the previous fiscal year. Most of these goals do not begin until FY 2005 or FY 2006 to allow the Agency time to hire and train new staff and construct review program infrastructures.

Performance Commitments. In addition to the performance goals, MDUFMA holds FDA to several commitments related to the medical device review process. These include, for example, programs and activities related to the application of user fee revenues, guidance development for the modular PMA review program,⁵ and examination of FDA's bundling policy.⁶

Measuring Performance.⁷ Progress on MDUFMA's performance goals and commitments is measured in different ways, based on the type of goal or commitment. The following types of measures are used to capture FDA's progress on meeting MDUFMA's performance goals and commitments:

- **Quantitative Measures.** MDUFMA's performance goals (cycle and decision goals) are quantifiable; that is, progress can be measured and described primarily

⁵ See Appendix A, section I, paragraph L.

⁶ See Appendix A, section I, paragraph N.

⁷ See Appendix B for a more detailed description of performance measures.

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through standard statistics (for example, number of submissions, mean review time, median review time, and percent meeting a review time standard).

- **Descriptive Measures.** Alternatively, some MDUFMA commitments are more descriptive in nature. For these, progress is reported through narrative accounts outlining specific actions taken, in addition to any results attributed to those actions.

Receipt Cohort. All FDA review performance statistics are based on a receipt cohort. This methodology calculates performance statistics for submissions for the year they were received, regardless of when FDA ultimately acted on, approved, or cleared the submissions. A consequence of this approach is that the statistics shown for a particular year may change from one report to the next. This is because as time passes, FDA completes work on more and more submissions within a cohort. As more submissions are completed, the statistics for that year of receipt must be adjusted to reflect the new completions. Until all submissions in a cohort are completed, only a preliminary performance assessment can be provided for that cohort.

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Original PMAs/PMRs and Panel-track PMA Supplements

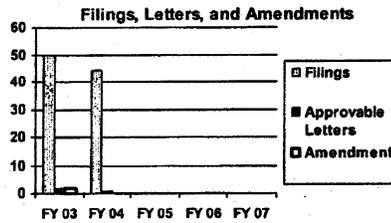
Goal – Act on an amendment containing a complete response to an “approvable” letter

The MDUFMA goal for actions on amendments containing a complete response to an “approvable” letter applies to original PMAs, Premarket Reports (PMRs), and Panel-track PMA Supplements. MDUFMA requires FDA to review and act on 90 percent of amendments containing a complete response to an “approvable” letter within 30 days. The table below summarizes the review time goal for such amendments.

Amendment Type	Review Time Goal	Performance Goal FY 2003 – FY 2007 Submissions
Original PMAs/PMRs	30 days	90% on time
Panel-track PMA Supplements		

Workload

The total number of PMAs/PMRs and panel-track PMA supplements filed in FY 2004 dropped when compared to FY 2003. Only two amendments to approvable letters have been submitted; both were for submissions filed in FY 2003.



Filings, Letters, and Amendments					
Type	FY 03	FY 04	FY 05	FY 06	FY 07
Total Filings (Original PMAs and PMRs/ Panel-track PMA Supplements)	50 (43/7)	44 (39/5)	--	--	--
Approvable Letters	2	1	--	--	--
Amendments	2	0	--	--	--

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Original PMAs/PMRs and Panel-track PMA Supplements

Performance

FY 2003 Submissions

FDA filed 43 PMAs and PMRs, seven panel-track PMA supplements and issued two "approvable" letters as of September 30, 2004 for FY 2003 submissions. FDA received a complete response amendment to these two "approvable" letters and responded to one within the 30 days allowed under this performance goal. With submissions still pending, it is too early to make a final determination for FY 2003.

FY 2003 Submissions					
Submission Type	Review Within	Reviewed and Acted On	Number on Time	MDUFMA Performance Goal	Percent on Time
Amendment containing a complete response to an "approvable" letter	30 days	2	1	90%	50%

FY 2004 Submissions

As of September 30, 2004, FDA had not issued any "approvable" letters for applications in this cohort, and had not had an opportunity to receive any amendments containing a complete response to the FDA "approvable" letter. With submissions still pending, it is too early to make a final determination for FY 2004.

FY 2004 Submissions					
Submission Type	Review Within	Reviewed and Acted On	Number on Time	MDUFMA Performance Goal	Percent on Time
Amendment containing a complete response to an "approvable" letter	30 days	0	0	90%	--

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Expedited Original PMAs

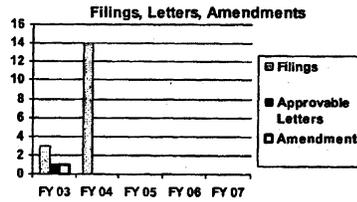
Goal – Act on an amendment containing a complete response to an “approvable” letter

The MDUFMA goal for actions on amendments containing a complete response to an “approvable” letter applies to expedited original PMAs and is identical to the goal for original PMAs/PMRs and Panel-track PMA Supplements. MDUFMA requires FDA to review and act on 90 percent of amendments containing a complete response to an “approvable” letter within 30 days. The table below summarizes the review time goal for such amendments.

Amendment Type	Review Time Goal	Performance Goal FY 2003 – FY 2007 Submissions
Expedited Original PMAs	30 days	90% on time

Workload

The number of expedited PMAs filed increased substantially in FY 2004. Only one amendment in response to an “approvable” letter has been submitted and was for a submission filed in FY 2003.



Filings, Letters, and Amendments					
Type	FY 03	FY 04	FY 05	FY 06	FY 07
Expedited Original PMAs	3	14	--	--	--
Approvable Letters	1	0	--	--	--
Amendments	1	0	--	--	--

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Expedited Original PMAs

Performance

FY 2003 Submissions

FDA filed three expedited PMAs and issued one "approvable" letter as of September 30, 2004 for FY 2003 submissions. FDA received a complete response amendment to this "approvable" letter and responded within the 30 days allowed under this performance goal; FDA ultimately approved that expedited PMA. With submissions still pending, it is too early to make a final determination for FY 2003.

FY 2003 Submissions					
Submission Type	Review Within	Reviewed and Acted On	Number on Time	MDUFMA Performance Goal	Percent on Time
Amendment containing a complete response to an "approvable" letter	30 days	1	1	90%	100%

FY 2004 Submissions

As of September 30, 2004, FDA had not issued an "approvable" letter for any expedited PMA in this cohort, and had not received any amendments containing a complete response to the FDA "approvable" letter. FDA approved one expedited PMA in this cohort without first issuing an "approvable" letter. With submissions still pending, it is too early to make a final determination for FY 2004.

FY 2004 Submissions					
Submission Type	Review Within	Reviewed and Acted On	Number on Time	MDUFMA Performance Goal	Percent on Time
Amendment containing a complete response to an "approvable" letter	30 days	0	0	90%	--

Additional MDUFMA Performance Commitments

This section reports on the additional commitments outlined in FDA's Commitment Letter. A detailed description of the commitments, performance targets, and definitions of terms can be found in Appendix A (section I, paragraphs I - P).

Maintenance of Current Performance

FDA's FY 2004 performance in review areas that do not have specific MDUFMA performance goals is comparable to FY 2003 and FY 2002 performance (performance prior to enactment of MDUFMA). The following table provides examples of sustained performance by product submissions.

CDRH Performance Indicators	FY 02	FY 03	FY 04
HDEs — Filing to first action (average FDA days)	53	39	44
HDEs — Elapsed time to approval (average FDA days)	60	44	57
IDEs — FDA review time (average FDA days)	28	27	28
IDEs — Percent of decisions made within 30 days	99%	100%	100%
IDE Amendments — FDA review time (average FDA days)	18	19	18
IDE Amendments — Percent of decisions made within 30 days	100%	100%	100%
IDE Supplements — FDA review time (average FDA days)	20	19	19
IDE Supplements — Percent of decisions made within 30 days	100%	100%	100%
CDER Performance Indicators	FY 02	FY 03	FY 04
BLA Supplements — CBE/CBE-30 — Percent of decisions made within 6 months	99%	97%	100%
PMA Supplements — CBE — Percent of decisions made within 180 days	100%	100%	100%
PMA Supplements — 135-day — Percent of decisions made within 135 days	NR	100%	100%
PMA Supplements — CBE-30 — Percent of decisions made within 30 days	67%	100%	100%
KEY: HDEs—Humanitarian Device Exemptions; IDEs—Investigational Device Exemptions; BLA—Biologic License Application; PMA—Premarket Application; CBE—Changes Being Effectuated; NR—None Received			

Some reported measures may change over time, as additional actions are taken on open applications.

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Meetings with Regulated Industry

FDA continues to encourage meetings as a particularly effective way to ensure that both FDA and applicants understand the clinical, scientific, and regulatory issues associated with new technologies. Pre-IDE and pre-PMA meetings have proven to be particularly beneficial and are used routinely by industry. During FY 2004, FDA reviewed more than 300 pre-IDE submissions and held more than 100 pre-IDE meetings. The more formal types of meetings (agreement meetings, determination meetings, 100-day meetings) are not used as frequently by premarket applicants. FDA is working to ensure that the need to meet MDUFMA's many quantitative performance goals (which require a great deal of focused attention) does not result in delays in scheduling and holding meetings with applicants.

Reviewer Training and Hiring

FDA is working to strengthen and expand its capacity to conduct efficient and timely reviews to ensure the safety and effectiveness of new medical devices. The Agency has made a good start towards hiring the additional staff that will be needed to improve the device review processes and meet the performance goals established for FDA under MDUFMA.

FDA was not able to hire new staff to implement MDUFMA until after FDA received its appropriation for FY 2003 on February 20, 2003. Prior to that time, FDA began implementing MDUFMA with existing staff. FDA's implementation of MDUFMA accelerated beginning with the second half of FY 2003, as FDA was able to begin hiring and training new staff. During FY 2004, FDA hired medical officers, consumer safety officers, chemists, microbiologists, biomedical engineers, statisticians, scientists, project managers, IT specialists, and other specialized staff. FDA also expanded the use of contractors and outside experts, providing additional flexibility to meet nonrecurring workloads, to augment FDA resources in highly specialized areas, and to achieve particular tasks at a lower cost than would otherwise be possible.

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- Resources Applied to MDUFMA Activities.** During FY 2003, CDRH increased the resources applied to the process for the review of device applications by 6 FTEs over FY 2002 while also constructing new program infrastructure for the review of device applications.⁸ During FY 2004, CDRH applied 54 more FTEs than FY 2003 (60

Process	FY 02	FY 03	FY 04	(Projected) FY 05
Premarket Review	529	534	575	660
Related Activities	146	147	160	167
Total	675	681	735	827
Increase Compared to FY 02	--	6	60	152

FTEs over FY 2002). CDRH projects that during FY 2005, 92 FTEs more than FY 2004 will be applied; this will mean CDRH will have increased the resources available to the process for the review of device applications by 152 FTEs since FY 2002.

For FY 2003, CBER received 11 FTEs for MDUFMA implementation.⁹ The process for the review of device applications required 58 FTEs. For FY 2004, CBER received an additional 9 FTEs for MDUFMA implementation, and estimated that the device review program required 67 FTEs. CBER has used MDUFMA resources to add medical and technical expertise in a variety of fields, such as infectious diseases, blood establishment computer software, blood collecting and processing devices, and blood banking reagents and equipment.

⁸ The "process for the review of device applications" is defined by section 737(5) of the FD&C Act.

⁹ CBER's regulatory responsibilities and workload demands are such that its personnel who are involved in medical device reviews are also expected to be involved with other workloads, such as biologics reviews. The 11 FTEs authorized for MDUFMA workloads will be spread over many new hires, each to work partly on device activities and partly on other workloads. Consequently, it is not appropriate to describe these new hires as being within a particular category of employee.

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- Hiring of New Personnel.** CDRH has hired almost all of its new personnel on term appointments. This approach is consistent with stakeholders' expectations that FDA will hire staff to meet critical needs as they arise and to meet those needs with a flexible approach that can be modified as the Agency's needs change. This approach also reflects the uncertainty surrounding MDUFMA funding.¹⁰

Hiring (category)/Number of Positions (not FTEs)		
Position	FY 03	FY 04
Scientist	26	19
Engineer	16	12
Statistician	6	9
Consumer Safety Officer	9	3
Medical Officer / Nurse	4	5
Project Manager	6	2
Program Support	7	5
Attorney	1	0
Total Hiring	75	55

- Medical Device Fellowship Program.** CDRH has established a Medical Device Fellowship program as a way to identify, recruit, and employ highly-specialized expertise. Participation in the program can be tailored to the interests of both CDRH and participants, making it a very flexible tool for meeting changing Center needs. As of October 1, 2004, 64 fellows were participating in the program.

Medical Device Fellowship Participation as of October 1, 2004	
Category	Participants
Engineers	42
Physicians	15
Scientists	5
Physicists	2
Total Participants	64

- Training.** CDRH and CBER have begun to train staff on the new guidance and procedures required to effectively implement MDUFMA, and have engaged in numerous training activities. Both Centers have also developed plans that will significantly increase clinical and technical training in the coming years.

Modular PMA Review Program

FDA issued initial guidance on modular PMA reviews in its guidance document, *Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products*, on February 25, 2003. This guidance explained that the

¹⁰ FDA's FY 2003 appropriation was delayed until February 2003, and the appropriations enacted for FY 2003 and FY 2004 were below the minimum levels required by section 738(g)(1) of the FD&C Act (this provision was added by section 102 of MDUFMA).

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fee for a modular PMA submission was due upon submission of the *first module* (not just the "shell" that described the overall plan for the modular submission).

On November 23, 2003, FDA provided a more comprehensive guidance document, *Premarket Approval Application Modular Review*; this guidance provided industry and FDA staff with information regarding the modular review program and outlined the procedures for submitting and reviewing a modular PMA. As FDA gains more experience with the modular PMA process, it will consult with stakeholders to develop performance goals for this program.

Note: FDA determined that it will not assess a MDUFMA review fee for any modular PMA submission whose first module was received prior to the statutory effective date of MDUFMA (October 1, 2002). FDA will receive additional modules for these PMAs for years to come, but will not receive any review fees for this considerable workload.

Bundling Policy

After consulting with stakeholders, FDA determined that bundling is appropriate under certain circumstances. On February 25, 2003, FDA issued initial guidance describing general bundling principles in its guidance document, *Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products*. This guidance explained that bundling may involve multiple devices or multiple indications for use in a single submission. On November 26, 2003, FDA provided a more comprehensive guidance document, *Bundling Multiple Devices or Multiple Indications in a Single Submission*. This guidance was intended to help industry and FDA staff understand when bundling may be appropriate, when separate submissions should be considered, and provided numerous examples illustrating these bundling principles for both 510(k) and PMA applications. Interest in bundling has increased since MDUFMA was enacted, and FDA is now receiving considerable numbers of bundled submissions.

Electronic Review of Applications

FDA published *Guidance for Industry. Providing Regulatory Submissions to CBER in Electronic Format - Investigational New Drug Applications (INDs)* (March 26, 2002), which applies to investigational studies of devices, such as blood screening test kits, leading to a BLA. CBER contributed to guidance documents on electronic submissions in general, and received a number of electronic submissions for biologic (non-device) reviews. To date, CBER has not received electronic submissions of any medical device applications.

CBER continues to make a significant outreach effort to inform regulated industry of the process for electronic submissions. In particular, during all sponsor meetings, CBER informs applicants and potential applicants of the ability to submit electronic documents. In addition, CBER is making provisions for secure e-mail when not associated with an original electronic application.

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CDRH is working with applicants to expand the use of electronic submissions, focusing first on increasing the use of electronic copies of applications. During FY 2004, CDRH received 48 submissions for PMAs, IDEs, 510(k)s, and other applications from 16 different sponsors entirely in electronic form. Instructions for making electronic submissions to CDRH are available at www.fda.gov/cdrh/elecsub.html. CDRH initiated a "Turbo 510(k)" pilot in the Office of In-Vitro Diagnostics Device Evaluation and Safety, providing an electronic template for submission and review of *in vitro* diagnostic device 510(k)s.

Preapproval Inspections

During FY 2003, FDA began a comprehensive examination of factors affecting the timeliness and efficiency of the preapproval inspection process to determine how the process can be improved and what resources would be required to make those improvements. During FY 2004, FDA continued to examine alternatives to improve the timeliness and efficiency of the process, and began to develop guidance to: 1) help industry better understand the preapproval inspection process, so they will be better prepared for their inspections; and 2) explain how the Centers will work with applicants, the Office of Regulatory Affairs, and with its field inspectors to improve the timeliness of preapproval inspections; this will include clearly-defined milestones in the preapproval inspection process to help ensure more timely scheduling and completion of inspections.

FDA expects to issue this guidance during FY 2005. The Agency expects the guidance, combined with associated process improvements, will help FDA meet both this goal and the PMA goals.

Next Steps to Implement MDUFMA Successfully

FDA faces a number of critical implementation steps in meeting MDUFMA's performance goals which grow progressively more challenging each year through FY 2007. These include building critical infrastructure, hiring and training additional staff, making greater use of external expertise, and reengineering our review processes to provide for more timely and efficient device reviews. Additionally, FDA will work with the Administration and Congress to ensure continued success of the device user fee program.

FDA needs to address the following implementation challenges to achieve the improvements promised by MDUFMA.

- Develop data systems that ensure each device review subject to a user fee is linked to the correct user fee payment and systems to measure FDA's review performance against the many goals established under MDUFMA. This will require new internal systems, as well as systems to link very different databases in FDA's Office of the Commissioner, CBER, and CDRH.

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- Move forward with electronic application submission and review systems and processes.
- Hire and train additional FDA scientists, engineers, statisticians, and other staff to: better distribute review workloads, expand the opportunity for meetings and other interaction with applicants, expand and update guidance documents used by applicants to prepare high-quality applications, and undertake the many additional efforts that will be required to meet or exceed MDUFMA's performance goals.
- Make greater use of external expertise to ensure timely action on medical device reviews that involve novel new technologies or unusual efforts.
- Ensure timely pre-approval inspections, both within the United States and abroad.
- Develop new processes for modular PMA reviews, and to work with stakeholders to develop meaningful performance goals for these reviews.
- Ensure that device reviews are completed in as few cycles as possible, thereby speeding the introduction of important new medical technologies and providing greater predictability in the reviews.

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**Appendix A: November 14, 2002, Commitment Letter from
DHHS Secretary Thompson to Congress**

THE SECRETARY OF HEALTH AND HUMAN SERVICES

Washington, DC, November 14, 2002

Hon. EDWARD KENNEDY
U.S. Senate
Washington, DC

DEAR MR. CHAIRMAN:

As you are aware, the Medical Device User Fee and Modernization Act of 2002 was signed by the President on October 26, 2002. Under Title I, the additional revenues generated from fees paid by the medical device industry will be used to expedite the medical device review process, in accordance with performance goals that were developed by the Food and Drug Administration (FDA) in consultation with the industry.

FDA has worked with various stakeholders, including representatives from consumer, patient, and health provider groups, and the medical device industry to develop legislation and goals that would enhance the success of the device review program. Title I of the Medical Device User Fee and Modernization Act of 2002 reflects the fee mechanisms and other improvements developed in these discussions. The performance goals referenced in Section 101 are specified in the enclosure to this letter, entitled "Performance Goals and Procedures." I believe they represent a realistic projection of what FDA can accomplish with industry cooperation and the additional resources identified in the bill.

This letter and the enclosed goals document pertain only to title I (Fees Related to Medical Devices) of Public Law 107-250, Medical Device User Fee and Modernization Act of 2002. OMB has advised that there is no objection to the presentation of these views from the standpoint of the Administration's program. We appreciate the support of you and your staffs, the assistance of other Members of the Committee, and that of the Appropriations Committees, in the authorization of this vital program.

Sincerely,

TOMMY G. THOMPSON

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MDUFMA PERFORMANCE GOALS AND PROCEDURES

The performance goals and procedures of the FDA Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER), as agreed to under the medical device user fee program in the Medical Device User Fee and Modernization Act of 2002, are summarized as follows:

I. REVIEW PERFORMANCE GOALS — FISCAL YEAR 2003 THROUGH 2007

All references to "days" mean "FDA days."

A. ORIGINAL PREMARKET APPROVAL (PMA), PANEL-TRACK PMA SUPPLEMENT, AND PREMARKET REPORT SUBMISSIONS

1. The following cycle goals apply to: 75% of submission received in fiscal year 2005; 80% of submissions received in fiscal year 2006; 90% of submissions received in fiscal year 2007.

- (a) First action major deficiency letters will issue within 150 days.
- (b) All other first action letters (approval, approvable, approvable pending good manufacturing practices (GMP) inspection, not approvable, or denial) will issue within 180 days.
- (c) Second or later action major deficiency letters will issue within 120 days.
- (d) Amendments containing a complete response to major deficiency or not approvable letters will be acted on within 180 days.

2. Decision Goals:

- (a) 80% of submissions received in fiscal year 2006 will have an FDA decision in 320 days.
- (b) 90% of submissions received in fiscal year 2007 will have an FDA decision in 320 days.

3. Subject to the following paragraph, 50% of submissions received in fiscal year 2007 will have an FDA decision in 180 days.

This goal will be re-evaluated following the end of fiscal year 2005. FDA will hold a public meeting to consult with its stakeholders and to determine whether this goal is appropriate for implementation in fiscal year 2007. If FDA determines that the goal is not appropriate, prior to August 1, 2006, the Secretary will send a letter to the Committee on Health, Education, Labor and pensions of the Senate and to the Energy and Commerce Committee, Subcommittee on Health of the House of Representatives stating that the goal will not be implemented and the rationale for its removal.

4. 90% of amendments containing a complete response to an approvable letter received in fiscal years 2003 through 2007 will be acted on within 30 days.

B. EXPEDITED ORIGINAL PMA SUBMISSIONS

1. The following goals apply to PMA submissions where:

- (a) FDA has granted the application expedited status;
- (b) The applicant has requested and attended a pre-filing review meeting with FDA;

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- (c) The applicant's manufacturing facilities are prepared for inspection upon submission of the application; and
 - (d) The application is substantively complete, as defined at the pre-filing review meeting.
2. The following cycle goals apply to: 70% of submissions received in fiscal year 2005; 80% of submissions received in fiscal year 2006; 90% of submissions received in fiscal year 2007.
- (a) First action major deficiency letters will issue within 120 days.
 - (b) All other first action letters (approval, approvable, approvable pending GMP inspection, not approvable, or denial) will issue within 170 days.
 - (c) Second or later action major deficiency letters will issue within 100 days.
 - (d) Amendments containing a complete response to major deficiency or not approvable letters will be acted on within 170 days.
3. Decision Goals:
- (a) 70% of submissions received in fiscal year 2005 will have an FDA decision in 300 days.
 - (b) 80% of submissions received in fiscal year 2006 will have an FDA decision in 300 days.
 - (c) 90% of submissions received in fiscal year 2007 will have an FDA decision in 300 days.
4. 90% of amendments containing a complete response to an approvable letter received in fiscal years 2003 through 2007 will be acted on within 30 days.

C. 180-DAY PMA SUPPLEMENT SUBMISSIONS

1. The following goals apply to: 80% of submissions in fiscal year 2005; 85% of submissions in fiscal year 2006; 90% of submissions in fiscal year 2007.
- (a) First action not approvable letters will issue within 120 days.
 - (b) All other first action letters (approval, approvable, approvable pending GMP inspection, or denial) will issue within 180 days.¹¹
 - (c) Amendments containing a complete response to a not approvable letter will be acted on within 160 days.
2. Decision Goals:
- (a) 80% of submissions received in fiscal year 2005 will have an FDA decision in 180 days.
 - (b) 80% of submissions received in fiscal year 2006 will have an FDA decision in 180 days.
 - (c) 90% of submissions received in fiscal year 2007 will have an FDA decision in 180 days.
3. Current performance for real-time review PMA supplement submissions will be maintained.

¹¹ This text was edited from the original version. "Not approvable" was taken out of the list of "All other first action letters." Because "Not approvable" letter is already captured under the "First Action" goal of 120 days, it should not be repeated under the "All other first actions" goal of 180 days.

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D. 510(k) SUBMISSIONS

1. The following goals apply to: 70% of submissions received in fiscal year 2005; 80% of submissions received in fiscal year 2006; 90% of submissions received in fiscal year 2007.

- (a) First action additional information letters will issue within 75 days.
- (b) Subsequent action letters will issue within 60 days.

2. Decision Goals:

- (a) 75% of submissions received in fiscal years 2005 and 2006 will have an FDA decision in 90 days.

3. Subject to the following paragraph, 80% of submissions received in fiscal year 2007 will have an FDA decision in 90 days.

This goal will be re-evaluated following the end of fiscal year 2005. FDA will hold a public meeting to consult with its stakeholders and to determine whether this goal is appropriate for implementation in fiscal year 2007. If FDA determines that the goal is not appropriate, prior to August 1, 2006, the Secretary will send a letter to the Committee on Health, Education, Labor and Pensions of the Senate and to the Energy and Commerce Committee, Subcommittee on Health of the House of Representatives stating that the goal will not be implemented and the rationale for its removal, and that the goal for fiscal year 2006 will be implemented for fiscal year 2007.

E. ORIGINAL BIOLOGICS LICENSING APPLICATIONS (BLAs)

The following goals apply to: 75% of submissions received in fiscal year 2006; 90% of submissions received in fiscal year 2007.

- 1. Review and act on standard original BLA submissions within 10 months of receipt.
- 2. Review and act on priority original BLA submissions within 6 months of receipt.

F. BLA EFFICACY SUPPLEMENTS

The following goals apply to: 75% of submissions received in fiscal year 2006; 90% of submissions received in fiscal year 2007.

- 1. Review and act on standard BLA efficacy supplement submissions within 10 months of receipt.
- 2. Review and act on priority BLA efficacy supplement submissions within 6 months of receipt.

G. ORIGINAL BLA AND BLA EFFICACY SUPPLEMENT RESUBMISSIONS

The following goals apply to: 75% of submissions received in fiscal year 2005; 80% of submissions received in fiscal year 2006; 90% of submissions received in fiscal year 2007.

- 1. Review and act on Class 1 original BLA and BLA efficacy supplement resubmissions within 2 months of receipt.
- 2. Review and act on Class 2 original BLA and BLA efficacy supplement resubmissions within 6 months of receipt.

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H. BLA MANUFACTURING SUPPLEMENTS REQUIRING PRIOR APPROVAL

The following goal applies to: 75% of submissions received in fiscal year 2006; 90% of submissions received in fiscal year 2007.

Review and act on BLA manufacturing supplements requiring prior approval within 4 months of receipt.

I. ADDITIONAL EFFORTS RELATED TO PERFORMANCE GOALS

The Agency and the regulated industry agree that the use of both informal and formal meetings (e.g., determination and agreement meetings, informal pre-investigational device exemption (IDE) meetings, pre-PMA meetings, pre-PMA filing meetings) by both parties is critical to ensure high application quality such that the above performance goals can be achieved.

J. MAINTENANCE OF CURRENT PERFORMANCE

It is the intent of the Agency that in review areas where specific performance goals have not been identified, current performance will be maintained.

K. APPLICATION OF USER FEE REVENUES

The Agency intends to apply significant user fee revenues to support reviewer training and hiring and/or outside contracting to achieve the identified performance goals in a responsible and efficient manner.

L. MODULAR PMA REVIEW PROGRAM

The Agency intends to issue guidance regarding the implementation of new section 515(c)(3) of the Federal Food, Drug, and Cosmetic Act. It is the intent of the Agency that once this program is implemented, the Agency will work with its stakeholders to develop appropriate performance goals for this program. Until such time, the Agency intends to review and close complete modules that are submitted well in advance of the PMA submission as expeditiously as possible.

M. "FOLLOW-ON" LICENSED DEVICES

The Center for Biologics Evaluation and Research will, if feasible, identify a category of "follow-on" licensed devices and collect information to determine whether alternative performance goals for such a category are appropriate.

N. BUNDLING POLICY

The Agency will, in consultation with its stakeholders, consider the issue of bundling for products with multiple related submissions. After such consultation, the Agency will either issue guidance on bundling or publish a notice explaining why it has determined that bundling is inappropriate.

O. ELECTRONIC REVIEW OF APPLICATIONS

The Agency will continue its efforts toward development of electronic receipt and review of applications, as expeditiously as possible, acknowledging that insufficient funding is included in the user fee program for this effort.

P. PREAPPROVAL INSPECTIONS

The Agency will plan to improve the scheduling and timeliness of preapproval inspections. The Agency will monitor the progress of these efforts and provide such information in the annual performance report.

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II. ANNUAL STAKEHOLDER MEETING

Beginning in fiscal year 2004, FDA will hold annual public meetings to review and evaluate the implementation of this program in consultation with its stakeholders.

III. DEFINITIONS AND EXPLANATION OF TERMS

A. For original PMA submissions, Panel-Track PMA supplement submissions, expedited original PMA submissions, 180-day supplement submissions, and premarket report submissions, issuance of one of the following letters is considered to be an FDA decision:

1. approval
2. approvable
3. approvable pending GMP inspection
4. not approvable
5. denial

B. For 510(k) submissions, issuance of one of the following letters is considered to be an FDA decision:

1. substantially equivalent (SE)
2. not substantially equivalent (NSE)

C. Submission of an unsolicited major amendment to an original PMA submission, Panel-Track PMA supplement submission, expedited original PMA submission, 180-day supplement submission, or premarket report submission extends the FDA decision goal date by the number of days equal to 75% of the difference between the filing date and the date of receipt of the amendment. The submission of the unsolicited major amendment is also considered an action that satisfies the first or later action goal, as applicable.

D. For BLA (original, efficacy supplement, or manufacturing supplement) submissions, the term "review and act on" is understood to mean the issuance of a complete action letter after the complete review of a filed complete application. The action letter, if it is not an approval, will set forth in detail the specific deficiencies and, where appropriate, the actions necessary to place the application in condition for approval.

E. For original BLA and BLA efficacy supplement resubmissions:

1. Class 1 resubmitted applications are applications resubmitted after a complete response letter that include the following items only (or combinations of these items):
 - (a) Final printed labeling
 - (b) Draft labeling
 - (c) Safety updates submitted in the same format, including tabulations, as the original safety submission with new data and changes highlighted (except when large amounts of new information including important new adverse experiences not previously reported with the product are presented in the resubmission)
 - (d) Stability updates to support provisional or final dating periods
 - (e) Commitments to perform Phase 4 studies, including proposals for such studies
 - (f) Assay validation data
 - (g) Final release testing on the last 1-2 lots used to support approval
 - (h) A minor reanalysis of data previously submitted to the application (determined by the agency as fitting the Class 1 category)
 - (i) Other minor clarifying information (determined by the Agency as fitting the Class 1 category)
 - (j) Other specific items may be added later as the Agency gains experience with the scheme and will be communicated via guidance documents to industry.
2. Class 2 resubmissions are resubmissions that include any other items, including any item that would require presentation to an advisory committee.

Appendix B: Measuring Performance Under MDUFMA

Different types of performance goals require different types of performance measures. FDA measures its success in meeting MDUFMA's goals and commitments in two ways: using *quantitative* measures and using *descriptive* measures, depending on how the objective for a particular performance goal is described in FDA's commitment letter. If the commitment letter provides an objective standard against which to measure our progress, we use quantitative measures. If the commitment letter does not provide an objective standard, FDA uses descriptive measures.

Quantitative Measures

Quantitative progress is measured and described primarily through standard, quantifiable statistics (for example, number of submissions, mean performance, median performance, percent meeting a review time standard). Each quantitative goal has the following characteristics:

- a clear definition of the submissions to which the goal applies (e.g., expedited PMAs),
- a clear definition of the action FDA is to take (e.g., issue a first action major deficiency letter),
- an objective review time standard (i.e., the number of days or months within which FDA is expected to take action),
- a quantifiable measure of performance (i.e., the minimum percent of submissions for which FDA is expected to meet the review time standard), and
- a specific time frame within which the goal applies (i.e., the fiscal year for which FDA performance will be evaluated).

MDUFMA's review performance goal progress is measured using quantitative methods.¹² Most of these goals use measures of success that become significantly more challenging over time.¹³ This approach recognizes that FDA must first hire and train new staff and rebuild review program infrastructures before it will be possible to make substantial progress in improving overall review performance, while providing interim goals that allow periodic evaluation of FDA's progress towards the ultimate goals of the program.

¹² These are defined in section I, paragraphs A through H, of FDA's Commitment Letter. A tabular summary of all of MDUFMA's objective performance goals is provided in Attachment C.

¹³ For example, Section I, paragraph B, goal 3(a) of FDA's Commitment Letter sets the following goal for Expedited PMAs: "70% of submissions received in fiscal year 2005 will have an FDA decision in 300 days." This is a quantitative goal because it applies to a defined category of applications (expedited PMAs), involves a defined type of action (an FDA decision), sets an objective review time standard (300 days), has a quantifiable measure of successful performance (70% of submissions), and applies within a specific time frame (FY 2005).

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Example: An example of where a performance goal is evaluated through quantitative measures is an Expedited PMA, received during FY 2005, when FDA's first action is a "major deficiency" letter. FDA will take that action (issue the letter) within 150 days of receipt of the Expedited PMA [(FDA Commitment Letter, section I, paragraph B, Item 2(a))].

Descriptive Measures

When quantitative measure cannot be used to evaluate FDA's progress in implementing a performance goal, the Agency uses descriptive measures to assess its performance. The Agency reports its progress in narrative accounts that outline the specific actions FDA has taken, the results are attributed to those actions.

MDUFMA's commitments use descriptive measures to assess performance.¹⁴ For descriptive measures, progress is reported through narrative accounts outlining specific actions taken, in addition to any results attributed to those actions. Descriptive measures:

- do not involve an objective review time standard
- do not have a quantifiable measure of successful performance, and
- do not specify the time frame within which it must be completed.

FDA regards all of MDUFMA's descriptive performance commitments to be in effect beginning with FY 2003 and will report progress towards achieving these commitments each year in the annual performance report.

Example: An example of where a performance goal is evaluated using descriptive measures is when FDA issues guidance on modular reviews under section 515(c)(3), and works with stakeholders to develop appropriate performance goals for the modular review program [(FDA Commitment Letter, section I, paragraph L)].

Receipt Cohorts

FDA measures its performance against applications in a *receipt cohort*. This methodology records performance on a submission in the statistics for the year it was *received*, regardless of when FDA ultimately acted on, approved, or cleared that submission. A consequence of this approach is that the statistics shown for a particular year may change from one report to the next. This is because, as time passes, FDA completes all work on more and more submissions. As more submissions are completed, the statistics for that year of receipt must be adjusted to reflect the new completions.

¹⁴ Defined in section I, paragraphs I through P, of FDA's Commitment Letter.

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Eligible Submissions Under MDUFMA

The performance goals of MDUFMA do not apply to device submissions received prior to FY 2003. Although FDA will work diligently to improve review performance for *all* applications, regardless of when they were received, submissions received prior to FY 2003 will not be reflected in the *performance statistics* used to evaluate FDA's progress towards meeting MDUFMA's goals. Submissions received since the start of FY 2003 (October 1, 2002) are subject to MDUFMA's performance goals, and will be reflected in FDA's performance statistics.

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Appendix C: Summary of MDUFMA's Quantitative Goals

This table summarizes all of MDUFMA's quantifiable review performance goals (section I, goals A through H, in DHHS Secretary Thompson's November 14, 2002, Commitment Letter).

Activity	Review Time	Performance Level (by FY) (— indicates no quantitative goal)				
		2003	2004	2005	2006	2007
PMAs, Panel-Track Supplements, Premarket Reports						
• FDA decision (approval, approvable, approvable pending GMP inspection, not approvable, denial)	320 days	—	—	—	80%	90%
• FDA decision – median performance	180 days	—	—	—	—	50% ¹⁵
• First action – "major deficiency" letter	150 days	—	—	75%	80%	90%
• First action – all other first actions (approval, approvable, approvable pending GMP inspection, not approvable, or denial)	180 days	—	—	75%	80%	90%
• Second or later action – "major deficiency" letter	120 days	—	—	75%	80%	90%
• Action on an amendment containing a complete response to a "major deficiency" or "not approvable" letter	180 days	—	—	75%	80%	90%
• Action on an amendment containing a complete response to an "approvable" letter	30 days	90%	90%	90%	90%	90%
Expedited PMAs These goals apply when FDA has granted expedited status; the applicant has attended a pre-filing meeting; manufacturing facilities are ready for inspection; and the PMA is substantively complete as defined at the pre-filing meeting.						
• FDA decision (approval, approvable, approvable pending GMP inspection, not approvable, denial)	300 days	—	—	70%	80%	90%
• First action – "major deficiency" letter	120 days	—	—	70%	80%	90%
• First action – all other first actions (approval, approvable, approvable pending GMP inspection, not approvable, or denial)	170 days	—	—	70%	80%	90%
• Second or later action – "major deficiency" letter	100 days	—	—	70%	80%	90%
• Action on an amendment containing a complete response to a "major deficiency" or "not approvable" letter	170 days	—	—	70%	80%	90%
• Action on an amendment containing a complete response to an "approvable" letter	30 days	90%	90%	90%	90%	90%

¹⁵ These goals will be re-evaluated following the end of FY 2005. FDA will hold a public meeting to consult with its stakeholders and to determine whether this goal is appropriate for implementation in FY 2007. If FDA determines that a goal is not appropriate, prior to August 1, 2006, the Secretary will send a letter to the Committee on Health, Education, Labor and Pensions of the Senate and to the Energy and Commerce Committee, Subcommittee on Health of the House of Representatives stating that the goal will not be implemented and the rationale for its removal.

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Activity	Review Time	Performance Level (by FY) (— indicates no quantitative goal)				
		2003	2004	2005	2006	2007
180-day PMA Supplements						
• FDA decision (approval, approvable, approvable pending GMP inspection, not approvable, denial)	180 days	—	—	80%	80%	90%
• First action – "not approvable" letter	120 days	—	—	80%	85%	90%
• First action – all other first actions (approval, approvable, approvable pending GMP inspection, or denial)	180 days	—	—	80%	85%	90%
• Action on an amendment containing a complete response to a "not approvable" letter	160 days	—	—	80%	85%	90%
510(k)s						
• FDA decision (SE/NSE)	90 days	—	—	75%	75%	80% [†]
• First action – "additional information" letter	75 days	—	—	70%	80%	90%
• Second or later action	60 days	—	—	70%	80%	90%
Biologics Licensing Applications - BLAs						
• Review and act on standard original BLAs (issue "complete action" letter)	10.0 months	—	—	—	75%	90%
• Review and act on priority original BLA submissions (issue "complete action" letter)	6.0 months	—	—	—	75%	90%
BLA Supplements						
• Review and act on standard BLA efficacy supplements (issue "complete action" letter)	10.0 months	—	—	—	75%	90%
• Review and act on priority BLA efficacy supplements (issue "complete action" letter)	6.0 months	—	—	—	75%	90%
• Review and act on BLA manufacturing supplements that require prior approval (issue "complete action" letter)	4.0 months	—	—	—	75%	90%
BLA Resubmissions, BLA Supplement Resubmissions						
• Review and act on a Class 1 resubmission to an original BLA or BLA efficacy supplement (issue "complete action" letter)	2.0 months	—	—	75%	80%	90%
• Review and act on a Class 2 resubmission to an original BLA or BLA efficacy supplement (issue "complete action" letter)	6.0 months	—	—	75%	80%	90%

Note: Definitions for the terms used here are provided in Section III of the FDA's Commitment Letter.

Appendix D: Glossary

Class – Each generic type of device is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device: Class I - General Controls, Class II - General Controls and Special Controls, and Class III - General Controls and Premarket Approval.

Humanitarian Device Exemption (HDE) – An application that is similar to a premarket application (PMA), but exempt from the effectiveness requirements of a PMA. An approved HDE authorizes marketing of a Humanitarian Use Device (HUD).

Investigational Device Exemption (IDE) – An IDE allows an investigational device to be used in a clinical study.

Modular Review Program for Premarket Applications (PMAs) – A mechanism by which an applicant may submit preclinical data and manufacturing information for review while still collecting, compiling, and analyzing the clinical data. A modular PMA is a compilation of sections or “modules” submitted at different times that together become a complete application.

Panel-track PMA Supplement – A supplemental application to an approved PMA or premarket report that requests a significant change in design or performance of the device, or a new indication for use of the device, and for which clinical data are generally necessary to provide a reasonable assurance of safety and effectiveness.

Premarket Application (PMA) – An application providing scientific and medical data to show that a Class III medical device is reasonably safe and effective for its intended use.

Premarket Notification [510(k)] – An application that demonstrates that the medical device to be marketed is substantially equivalent (SE) to a legally-marketed device that was or is currently on the U.S. market.

- **Substantially Equivalent (SE)** – A device is substantially equivalent to a legally marketed device.
- **Not Substantially Equivalent (NSE)** – A device is not substantially equivalent to the already legally marketed device.

Premarket Report (PMR) – A type of premarket application for a reprocessed single-use device.

Product Development Protocol (PDP) – An alternative to a PMA, based on early consultation between the sponsor and the FDA, that leads to a device development and testing plan acceptable to both parties. It minimizes the risk that the sponsor will pursue the development of a device that FDA will not approve.

MEDICAL DEVICE USER FEES

Question. During operation of the medical device user fee program, has the agency been able to determine specific direct and indirect costs of performing the various types of PMA and 510(k) device approvals? Will FDA be able to determine incremental direct and indirect costs that will be associated with improving review times under more aggressive performance goals in the future?

Answer. FDA is engaging with industry and stakeholders as we work on the MDUFMA reauthorization. If the MDUFMA reauthorization results in changes to the performance goals, we will be able to estimate direct and indirect costs. During fiscal year 2005, FDA contracted with Dr. Dale R. Geiger, a recognized expert in the field of government cost accounting, to prepare a report of the costs of FDA medical device review processes. The statement of work for this report did not require Dr. Geiger to make findings and conclusions. Rather, Dr. Geiger prepared analysis for FDA to consider during the MDUFMA reauthorization. Dr. Geiger examined FDA medical device reviews conducted during fiscal year 2003 and fiscal year 2004, including investigational device exemption applications, investigational new drug applications, premarket approval applications, or PMAs, PMA supplements, biologics licensing applications, or BLAs, BLA supplements, and 510(k) premarket notifications.

The methodology employed by Dr. Geiger follows generally accepted accounting principles for U.S. Government reporting entities, and parallels the methodology applied by an earlier Arthur Anderson study that measured PDUFA costs for 1992 and 1993. Dr. Geiger examined both direct and indirect costs, at CBER, CDRH, the Office of Regulatory Affairs, or field, and FDA general and administrative costs. This work will assist FDA with cost analysis in regards to the performance goals resulting from the MDUFMA reauthorization.

Question. What criteria does the agency use to determine the allocation and priority for distribution of staff increases across FDA components, including offices, divisions, branches, regions, and districts resulting from medical device user fees and related Congressional appropriations?

Answer. In the absence of a Congressional directive, FDA allocates medical device user fees and other medical device appropriations to best achieve FDA's public health objectives, the performance goals, and other expectations established under the Medical Device User Fee and Modernization Act of 2002 and its amendments. Resources have been allocated to reflect the workload balance between the Center for Devices and Radiological Health, or CDRH, and the Center for Biologics Evaluation and Research, or CBER. Soon after MDUFMA was enacted, FDA estimated that 83 percent of the device review work was performed in CDRH and 17 percent was performed in CBER. The field resources associated with each Center are included in these percentages. FDA's fiscal year 2003 to fiscal year 2005 allocations were based on these percentages. FDA is presently reexamining this allocation and expects this examination will result in a higher percentage of MDUFMA being allocated to CDRH.

Field resources are allocated among districts by the Office of Regulatory Affairs, or ORA, according to each district's projected medical device workload. To illustrate the use of workload to determine distribution of resources, CDRH's MDUFMA hiring priorities were established by product group experts who made recommendations about the type and order of new hires that would best contribute to improving the device review process. For example, the CDRH cardiovascular group, which included experts on those types of devices from across the Center, concluded that their highest priority for improving and speeding the review of cardiovascular devices were additional statisticians. Other product review teams—for example, those for in vitro diagnostic devices, ophthalmic and ENT devices, ob-gyn, gastro-renal, and urological devices—identified the priority needs they believed were essential to improving the quality and timeliness of the review process.

POSTMARKET SAFETY ISSUES

Question. At the industry-agency workshop on ongoing efforts to improve post-market safety activities in February of this year, several issues came up that are of potential concern.

With regard to the notion of requiring "unique product identifiers," how would this requirement differ from and improve on the existing device tracking requirements for high risk devices? What technical and labeling issues arise with regard to such a requirement for all devices?

Answer. The device tracking requirement applies to manufacturers of a small set of mostly implantable devices, and intends to ensure that manufacturers can quickly locate defective devices and notify patients. Conversely, the idea underlying unique

device identification, or UDI, is to require manufacturers to apply a unique code to the label of a variety of medical devices, in both human and machine readable formats, like barcodes. When combined with other health information technology efforts, UDI has the potential to provide a number of benefits to improve patient safety. Important potential benefits include the reduction of device-related medical errors through the recognition of compatibility and interoperability issues; facilitating the population of device information in patients' electronic health records; and improving the accuracy of information about marketed devices through the standardized identification of specific devices in adverse event reports. Additionally, an effective system of device identification should allow more efficient recall of defective devices and also assist in fighting counterfeit devices.

The type of information included in the UDI will determine what technical and labeling issues arise. FDA is currently considering the appropriate scope of such information and intends to address these issues in a rulemaking.

Question. With regard to the draft guidance document on requirements for additional information to be included in annual reports, does FDA already have this information in various formats and disparate offices throughout the device center? Would it make more sense for the agency to break down its internal barriers that prevent effective utilization of information already collected by the Center for Devices and Radiological Health?

Answer. The Center for Devices and Radiological Health, also known as CDRH, believes that data and information gathered in the postmarket setting is critical to our continued confidence in the safety and effectiveness of marketed devices. Pre-market Approval, or PMA, annual reports are one of the important tools that FDA relies upon to gather information about the device once it is marketed. For this reason, CDRH is assessing the information provided in annual reports to ensure that these submissions provide meaningful information for the agency and industry to assure postmarket safety. At this time, CDRH has not made a final decision as to the type of information that should be included in a PMA annual report. Once the decision is made, CDRH will take the necessary steps to ensure that the information required in the annual report is not duplicative of other regulatory reporting requirements.

CDRH is also reviewing our internal processes and systems for communicating post-market information across the center. As part of its on-going effort to improve all aspects of post-market safety, CDRH initiated the Postmarket Transformation Leadership Team that consists of CDRH managers and external experts to guide the Center in this effort.

CRITICAL PATH INITIATIVE

Question. FDA is requesting an increase of \$5.9 million for the Critical Path Initiative. This funding is specified for the Center for Drug Evaluation and Research. However, I understand that the Critical Path Initiative is intended to speed the development of all medical products regulated by FDA.

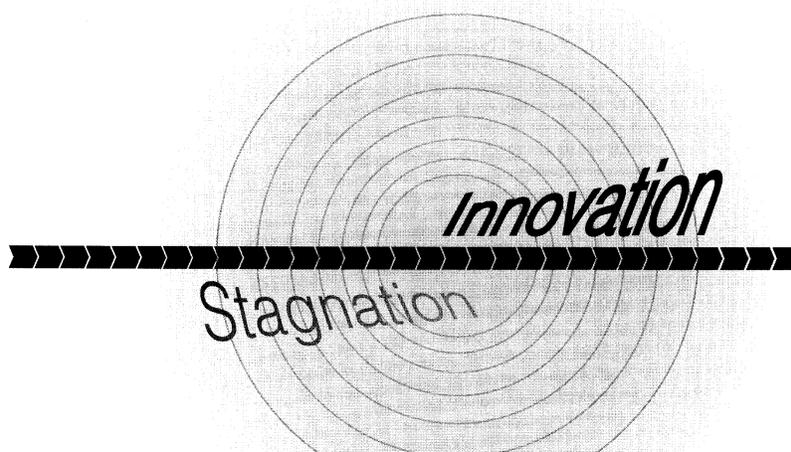
Will the requested funding be made available to other FDA Centers? If so, how much will be made available to each FDA center?

Answer. All FDA centers will participate in Critical Path activities in order to achieve the public health benefits envisioned by FDA in its Critical Path report of March 16, 2004, and the Critical Path Opportunities List announced on March 16, 2006. In fact, several of the projects described in our budget request are cross-center projects, such as work to create a library of digital electrocardiograms, also known as ECGs, that involves both the Center for Drug Evaluation Research and the Center for Devices and Radiological Health.

The Agency is still working with our partners in government, academia, and industry to determine which Critical Path activities, in addition to those identified in our fiscal year 2007 budget request, are the most appropriate activities to fund in fiscal year 2007.

I would be happy to provide for the record the Critical Path Opportunities List that was announced on March 16, 2006.

[The information follows:]



Innovation

Stagnation

**Critical Path
Opportunities List**

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Critical Path Opportunities List

INTRODUCTION

This report is divided into two parts. The first part of the report (the Critical Path Report and Opportunities List) discusses what has been learned about the opportunities and challenges along the Critical Path from stakeholders and FDA scientists since the publication in March 2004 of the FDA Critical Path Report. The second part of the report (the Opportunities List) presents specific opportunities that, if implemented, can help speed the development and approval of medical products. Both documents are available individually on the FDA's Web site (<http://www.fda.gov/oc/initiatives/criticalpath/>).

TOPIC 1: BETTER EVALUATION TOOLS

Developing New Biomarkers and Disease Models to Improve Clinical Trials and Medical Therapy

Biomarker Qualification and Standards

1. Biomarker Qualification. The process and criteria for qualifying biomarkers for use in product development should be mapped. Clarity on the conceptual framework and evidentiary standards for qualifying a biomarker for various purposes would establish the path for developing predictive biomarkers. Stakeholders, including industry, researchers, and patient groups would have a clear idea of what needs to be done to adopt a new biomarker for regulatory use. Such a framework could stimulate biomarker development and, consequently, shorten the time necessary to develop a successful marketing application.

Identifying the framework and evidence needed to qualify biomarkers for different purposes would put an emphasis on correlative and predictive science to accompany the current emphasis on biomarker discovery. Consensus on the following types of questions is needed to put such a framework in place:

- How can biomarker evidence help demonstrate that a candidate product is not too toxic to test in humans?
- How can biomarkers be used to select dose ranges for initial human testing?
- How can biomarkers be used most effectively to evaluate dose response in later trials?
- What biomarker evidence is appropriate to guide selection of patients for clinical testing?
- What types and levels of evidence are needed to accept a biomarker as a surrogate endpoint for product efficacy?

Similarly, a framework for co-development of a drug and its partner diagnostic could promote biomarker

development and facilitate integration of personalized medicine into clinical practice.

2. Standards for Microarray and Proteomics-Based Identification of Biomarkers. Microarray and proteomic technologies hold vast potential to identify biomarkers. However, a gap exists between technologies in use today and the technological level required for their application during product development and regulatory decision making. This gap results from the limited availability of accepted standards for demonstrating comparability of results, for data normalization and analysis, for validation of array results, or for biological interpretation of significant gene expression changes or mutations. Reference RNA samples that could be used to standardize biomarker results would improve the use of microarray technologies during product development, as would standards for RNA and DNA extraction methodologies and for RNA conversion and labeling. Standards for human tissue RNA and external RNA controls (sometimes referred to as *spikes*) are under development, but standards for the other steps associated with the analysis and interpretation of hybridization data still need to be addressed.

Qualifying Disease- and Disorder-Specific Biomarkers

Asthma**3. Role of Beta Adrenergic Receptor**

Polymorphisms in Asthma Treatments. In clinical trials of beta agonists in asthma patients, polymorphisms of the beta adrenergic receptor seem to predict short-term patient deterioration, but information on long-term consequences has not been developed. Studies to evaluate whether receptor status predicts long-term outcomes could help target treatment in this disorder (possibly to avoid serious side effects) and help sponsors develop and test new therapies.

Pregnancy**4. Measures of Effectiveness of Fertility**

Treatments. Although number of pregnancies and newborns can serve as rough measures of effectiveness, no reliable markers exist for ovulation induction (e.g., hormone levels, ultrasound determination of follicular development) or other potential predictors of successful pregnancy that could allow early assessment of therapy during product testing and early adjustment of therapy during treatment. Such markers could improve fertility treatment outcomes and reduce toxicity.

5. Markers of Effectiveness of Treatment for Pre-term Labor.

Delay of delivery is the standard measure of the effectiveness of treatments for pre-term labor. But what duration of delay time improves fetal and maternal outcomes? Valid biomarkers would decrease the time needed to study potential therapies, reduce unnecessary risk to study subjects, and help physicians determine the best treatment duration for their patients.

Cardiovascular Biomarkers

6. Surrogate Outcomes for Cardiovascular Drug Eluting Stents. A statistical model for qualifying late loss in lumen diameter as a surrogate measure for cardiovascular drug eluting stent trials could facilitate

the development of these products and enrich the understanding of their long-term effects.

7. Circulating Biomarkers in Cardiovascular Diseases. A large number of candidate biomarkers for cardiovascular diseases have been identified, but have not been proven useful for product development and regulatory purposes. For example, markers that identify patients at high risk for a cardiovascular event could rapidly improve trial efficiency for interventions intended to prevent such events. Trials could use biomarkers to stratify patient populations by risk status or to limit the study to high-risk patients. New markers that reflect tissue damage or acute inflammation (e.g., troponin sub-types, inflammatory cytokines) could help assess response to novel treatments more efficiently and aid in identifying products most likely to be successful in larger scale clinical trials.

Today, sponsors cannot reliably measure the effects of products intended to reduce inflammation in atherosclerosis without subjecting the patient to invasive procedures. This makes trial enrollment more difficult, increases patient risk and trial costs, and makes study of marketed products very difficult. Developing and qualifying a biomarker for these atherosclerotic inflammatory processes or other aspects of cardiovascular disease would improve innovation in a field affecting millions of Americans. Such markers could also be used in clinical practice to evaluate patient risk and to assist physicians and patients in developing treatment strategies.

Infectious Diseases

8. Proving the Efficacy of Preventive Vaccines. Proving the efficacy of preventive vaccines can be particularly costly, because of the need to study the disease-preventing effects of candidate vaccines in large numbers of subjects for long periods of time. If surrogate markers of protection, such as measurements of the immune response to vaccines, could be correlated with protection from disease, vaccines against influenza, SARS, West Nile Virus,

smallpox, hepatitis C, and parasitic infections could be developed more quickly and more cost effectively.

9. Markers of Disease Progression in Hepatitis C. Is Hepatitis C viral load in blood an accurate predictor of the pathologic changes and progression of liver disease in patients with Hepatitis C disease? How best can immune responses to the virus infection be distinguished from protective immunity due to vaccination for Hepatitis C? Progress toward more effective treatments and preventive vaccines for this disease could be enhanced with the development of a composite endpoint that includes serologic, virologic, and biochemical components.

10. Testing New Therapies for HIV Infection. Numerous therapeutic agents have been identified that may reconstitute immune function in patients with acquired immunodeficiencies; a serious barrier to their clinical development is the absence of well-understood markers of general immune competence that could predict clinical benefit. Preliminary evidence exists that host immune responses to immunization may serve as a valuable marker for evaluating immune-based therapy in HIV disease. A well-designed study testing the ability of a set of recall antigens and neoantigens to generate antibody responses and class I and class II MHC restricted T cell responses could identify markers that predict general immune competence in this population. Responses could be correlated with HIV viral load, a surrogate marker for clinical benefit in patients with HIV infection.

Cancer

11. Markers of Disease Progression in Prostate Cancer. There are no reliable biomarkers for disease progression in aggressive prostate cancer that have demonstrated utility in product development. Although prostate specific antigen (PSA) is used for a variety of purposes (e.g., determining when further diagnostic testing is indicated, assessing response to therapy), there is no consensus on how best to use PSA in cancer therapeutic trials. Uses of PSA that should be further investigated include identifying high-risk populations, providing an early marker of drug activity and dose range, and use of PSA as a marker of disease progression.

Other markers may also prove more predictive of clinical outcomes in some patients (e.g., alpha-methylacyl CoA racemase expression as a predictor of disease progression in local disease). A gap

analysis to rigorously identify what is proven and unproven about PSA and other potential indicators would be an important first step to improving prostate cancer biomarkers.

12. Drug Targets as Critical Path Tools: Cancer Therapies. Many molecules are being explored as targets for cancer therapy. For example, sponsors are increasingly focused on activity profiles of groups of such molecules associated with aberrant signaling in the proliferation and survival pathways recognized to be disturbed in many types of cancers, such as the SRC pathway and the P13K/Akt pathway. Similarly, cell surface antigens are being explored as targets. Diagnostic tests evaluating the status of therapeutic targets may prove to be useful markers to predict responsiveness to therapy. Availability of markers assessing the status of therapeutic targets would make development of targeted cancer therapies more effective and efficient.

Neuropsychiatric Diseases

13. Diagnostic Markers for Neuropsychiatric Conditions. Today, diagnosis of psychiatric disorders is based on symptom presentation. For example, there are no diagnostic tests to distinguish an initial presentation of depression from the onset of bipolar disorder or other conditions, or to differentiate various subsets of the autism currently joined under the rubric of pervasive developmental disorders. Identification of such markers would improve clinical trials by making it possible for sponsors to enroll only those patients with the target condition. Similarly, any successful treatments could better target a patient's disease in clinical practice. If specific aspects of mental disorders could be better quantitated, sponsors could test therapies targeted to a particular patient's constellation of symptoms. For example, now that the MATRICS test battery for assessing cognitive impairment in schizophrenia has been developed, we expect to see applications for drugs targeted to improving the cognitive component of this disease. Such targeting would both improve the efficiency of trials and serve to better individualize therapeutic approaches.

Presbyopia

14. Clinically Relevant Measures for Efficacy of Accommodating Intraocular Lenses. Presbyopia correction is currently limited to static devices (e.g., bifocal and reading glasses). The ophthalmic community is currently investigating methods to correct presbyopia by restoring active visual accommodation. However, current measurements of accommodation are subjective and unreliable. Identification of objective measures appropriate for clinical trials would improve sponsors' ability to evaluate the effectiveness of devices for the correction of presbyopia and allow reduced subject testing time.

Autoimmune and Inflammatory Diseases

15. Markers of Disease Activity in Systemic Lupus Erythematosus, Inflammatory Bowel Disease, and Related Diseases. Development of new therapies for these diseases has been hampered in recent years by a lack of reliable markers of disease activity that can be used to predict clinical benefit. Development of predictive biomarkers and accepted clinical outcome measures would help in the evaluation of needed new therapies for these diseases.

Safety Biomarkers

16. Predicting Adverse Reactions to Vaccines. Work to identify biomarkers that predict the development of adverse reactions to vaccines, such as autoimmune disease following therapeutic cancer vaccines, could speed the development of these therapies. Similarly, identification of biomarkers that predict the risk of developing enhanced disease following use of certain vaccines, such as SARS, could make such therapies more attractive to product developers.

17. Early Indicators of Effects of Immune Responses on the Safety of Cell and Tissue Products. The potential for these products to prevent or treat diseases is exciting and vast. With this potential benefit comes the risk of an immune response that reduces product efficacy and/or stimulates autoimmune disease. Years of product development can be wasted if a product triggers a detrimental immune response when finally tested in animals or humans. Better and earlier predictors of this undesirable immunogenicity would help unlock the potential of cellular and tissue products, by helping sponsors invest in product candidates least likely to trigger an unwelcome human immune response.

18. Predicting Cardiac Toxicity. New tools for early identification of cardiac toxicity would improve product development for a wide array of conditions. Research investments that could produce tangible benefits quickly include creation of an ECG library from clinical trials that could be used for identifying potential early predictors of cardiac risk.

19. Gene Therapy. Several gene therapy products have been successfully used in early human testing to treat severe diseases, including life-threatening inherited immune deficiencies. However, the future of these products is at risk due to the demonstrated potential for carcinogenesis. Biomarkers to predict the general risk or patient-specific risk for cancer and work to reduce these risks could improve product performance in long-term safety studies of these therapies.

20. Modernizing Predictive Toxicology. Identifying preclinical biomarkers that predict human liver or kidney toxicity would speed innovation for many different types of therapeutics. Activities to develop genomic biomarkers for the mechanistic interpretation of toxicological observations—complementary to but independent of these classic toxicological observations—could begin to create the data foundation for qualification of new safety biomarkers. Collaborations among sponsors to share what is known about existing safety assays could be a first step toward the goal of safer medical products.

 Advancing the Use of New Imaging Techniques
21. Performance Standards for Imaging Displays.

The ability to use imaging results as biomarkers would be enhanced by development of standards and performance assessment methods for displays used by newer imaging devices. Compared with older imaging technologies, the displays used by today's digital imaging technologies are complex; in some cases, they are miniaturized to facilitate remote and portable viewing. Common criteria that can assess the performance of multi-dimensional display devices for the presentation of dynamic volumetric image sets with color coding would enhance the understanding of and confidence in imaging results.

22. Using Medical Imaging as a Product Development Tool.

A key hurdle to using imaging as a biomarker in clinical trials is lack of standard protocols for using imaging technologies, ranging from patient positioning to instrument calibration to the settings used for particular images. As a result, sponsors and others cannot compare imaging results across trials, sometimes not even within a trial. This also means it is difficult or impossible to compile data needed to demonstrate that a particular technique correlates with clinical course sufficiently for use as a biomarker. Standard, publicly available, protocols for use of imaging in clinical trials would enable the development of biomarkers for a wide array of conditions.

23. Imaging Biomarkers in Cardiovascular Disease.

To advance efficient development of new therapies, new imaging techniques are needed to measure progression and treatment of cardiovascular disease. Examples include the potential use of intravascular ultrasound (IVUS), MRI, or multi-slice CT in the assessment of atherosclerosis progression and volumetric measures of cardiac function in trials of congestive heart failure. Development of these techniques for measuring progression will require a complete analysis of the current state of knowledge of the imaging modality, standardization of the technical aspects of the measurement, and performing the trials necessary to evaluate the degree of correlation with clinical responses.

24. Imaging Biomarkers in Arthritis.

Targeted research could identify how to apply MRI technologies to measure the effects of potential therapies on cartilage and joint soft tissue for rheumatoid arthritis and osteoarthritis. In this regard, MRI has demonstrated promise for detecting soft tissue inflammation and cartilage erosion in rheumatoid arthritis. If established as a reproducible biomarker, use of MRI could help determine the potential of a new therapeutic product, identify dose ranges, and stratify patients by risk while serving as an early response measure.

25. Imaging Biomarkers in Neurocognitive Diseases.

Currently, therapeutic trials in chronic neurologic disorders, such as Parkinson's disease and Alzheimer's disease, rely on symptomatic endpoints that may require observation over many years to evaluate progression. Functional imaging, such as FDG-PET as a measure of glucose metabolism, may provide a biomarker to assess earlier, more subtle, changes in the progression of these diseases. Studies would be needed to determine how these markers correlate with symptomatic progression. Focused efforts to apply new imaging techniques as diagnostic and response measures in neurocognitive disorders and depression could also produce new ways to monitor treatment of these conditions. For example, quantitative MRI measurements as well as amyloid content assessments by PET scan may be useful imaging techniques to demonstrate the effect of potential Alzheimer's therapies. Imaging markers that provide information on early disease states could make prevention trials more feasible. These approaches have not yet been proven clinically meaningful, however, and, in many cases, there is no consensus on the most promising approach.

26. Imaging in Cancer.

Cutting edge imaging techniques hold vast potential for tumor staging and assessing response to therapy. The list of promising biomarkers in need of qualification is long. For example, it is possible that one additional, well-designed study could qualify FDG-PET as an additional response measure in non-Hodgkins lymphoma, thus creating a new tool that improves both product testing and treatment decisions. Similar opportunities exist for other tumor types.

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27. Imaging in Chronic Obstructive Pulmonary Disease. High-resolution chest computed tomography may be a useful assessment of disease progression in chronic obstructive pulmonary disease where emphysema is a prominent component, especially the disease associated with alpha 1 anti-trypsin deficiency. Although data to date suggest that high-resolution CT (HRCT) can offer reliable assessment of underlying lung structure in fewer patients and for shorter periods of time than would be needed to show a difference in lung function testing or in mortality, it remains unclear if changes in HRCT meaningfully predict change for the patient. It also is unclear what level of change in the HRCT parameters could be considered significant in terms of disease modification. The ability to use HRCT demonstration of disease modification as an endpoint in clinical trials could pave the way for new product indications that are now infeasible due to the rarity of alpha 1 anti-trypsin deficiency and the trial size and duration needed to show an effect using traditional endpoints. New trials, perhaps with innovative designs, are needed to evaluate the use of imaging techniques in rare conditions.

28. Noninvasive Therapeutic Monitoring. Today, the distribution of a drug in the human body is typically evaluated by measuring its concentration in

the blood, which may not accurately reflect distribution to the target tissue (e.g., an infected bone, a tumor, or a malfunctioning organ). Noninvasive means of monitoring drug concentration, for example, using molecular tags that can be located through imaging techniques, could dramatically improve product development by enabling sponsors to correlate response with drug availability at the target site and to evaluate the relationship between organ toxicity and drug distribution to that organ.

29. Imaging Implanted Devices. *Practice guidelines* should be developed that outline the nature and frequency of imaging needed to follow the on-going safety and efficacy of an implanted device, when to suspect a problem, and what confirmatory tests are recommended. Such guidelines could not only improve patient safety but could also produce pooled data to inform premarketing development and testing of the next generation of implanted devices. (*Practice guidelines* are developed by professional associations on specific topics to help healthcare professionals make treatment decisions.)

Improving Predictions of Human Response from Disease Models

30. Improving Extrapolation from Animal Data to Human Experience. We urgently need new methods to bridge from animal data to predicted human experience, for both product efficacy and for product safety. The need is particularly acute for situations in which it is unethical to conduct human tests (e.g., therapies against bioterror agents). Establishing reliable correlations between animal pharmacokinetic/pharmacodynamic data and human outcomes would dramatically improve the safety of human testing and treatment and the ability of sponsors to invest in only those candidate products most likely to be effective in humans. Conversely, re-examination of existing data could identify features of preclinical studies that were not predictive of human response. We especially need more predictive preclinical models for therapies that use innovative delivery mechanisms (e.g., image guided interventional therapies, or local delivery of therapy

via percutaneous catheter) and for combination therapies.

31. Better Model of Wound Repair. The lack of a reliable animal model for human wound healing is a significant hurdle to developing new wound repair products.

32. Better Animal Disease and Tissue Injury Models. Better animal disease or tissue injury models could provide more accurate predictions of the toxicity of drugs, devices, and biological products that are used in ill or injured patients. Use of such models could also enhance our understanding of the potential toxic effects of compounds associated with many types of medical devices (some devices may expose patients to sterilants, disinfectants, plasticizers, and metals).

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33. Better Disease Models for Predicting Biological Product Toxicity. Better predictive disease models to support the development of more quantitative cellular, or molecular, toxicity testing paradigms for product safety evaluation would improve development of many biological products. For example, development of an in vitro cell-based system to evaluate and predict the toxicity of hemoglobin-based oxygen carriers would help identify some of the serious safety issues surrounding these products.

TOPIC 2: STREAMLINING CLINICAL TRIALS

Creating Innovative and Efficient Clinical Trials and Improved Clinical Endpoints

Advancing Innovative Trial Designs

34. Design of Active Controlled Trials. Many clinical trials compare two or more active therapies, rather than comparing an active therapy with placebo. This design is being increasingly used as more therapeutic choices become available. When treatment options exist, it may be unethical or infeasible to ask patients to take a placebo. Today, there is confusion regarding key statistical issues underlying design and analysis of active-controlled trials. In placebo controlled trials, the question is whether the active treatment is highly likely to be superior to placebo.

In active controlled trials, the question is often whether the new treatment is highly unlikely to be inferior to the comparator. Such trials are called non-inferiority trials. Statistical methods for demonstrating non-inferiority can be challenging. We need to reach agreement and clarify appropriate statistical methods and standards for such trials to facilitate product development in a wide array of conditions for which non-inferiority trials are used. Issues that need clarifying include:

- How should the confidence interval for demonstrating non-inferiority be determined?
- What data should be used to estimate the effect of the control agent (e.g., all prior studies)? How should they be weighted?
- What drugs should be included as the active control? How should inconsistent results (i.e., size of treatment effect) from prior studies of the active control be approached?
- What are appropriate sample size requirements in non-inferiority and active-controlled studies?

Non-inferiority trials rely in part on prior studies to estimate the assumed treatment effect of the comparator. In some conditions, however, only a single trial is required for drug approval. This is often the case for new cancer therapies. New methods for conducting non-inferiority trials are needed for cases when prior data are insufficient to estimate the effect of a therapy. For example, it might be possible to use biomarker data to circumvent some of these difficulties.

35. Enrichment Designs. If biomarkers can reliably identify individuals with a high probability of response to a therapy, trials could focus on such patients. Conducting a trial in a potential high-response subgroup is called *enrichment*. Enriched trials have greater power and could result in therapies targeted at those most likely to benefit. Enrichment raises some difficult issues:

- How will data on the marker status of potential trial enrollees be used in trial design?
- How much data are needed on the un-selected population?
- What types of retrospective subset analyses are valid (e.g., what can be reliably learned from subgroup analyses that were not prespecified in the original trial design)?

36. Use of Prior Experience or Accumulated Information in Trial Design.

Adaptive Trial Design

Stakeholders are looking for clear rules on when it is valid to make changes to a clinical trial protocol, based on early or interim study results, when unblinded treatment results may be known.

Consensus and clarification is needed on questions such as:

- When can extra trial arms be dropped?
- When can an early marker be used to choose which treatment to carry forward or to choose a subset for analysis?
- When is it valid to modify randomization based on results, for example, in a combined phase 2/3 cancer trial?
- When is it valid and under what situations can one stage or phase of a study be combined with the second stage or phase?

Non-Frequentist Methods

Statistical techniques that allow for increased reliance on historical data, under assumptions and models that can be justified, might be used to develop predictive inferences. The use of these techniques in product development holds promise, but work remains to adapt and qualify such methods for use to answer specific product development questions for both clinical and preclinical applications. For example, we urgently need to improve use of animal data to predict human experience (see Opportunity 30). Many believe that Bayesian and similar non-frequentist statistical methods that use empirically derived prior information and models to develop predictive probabilities could provide a basis for supplementing the traditional methods for human equivalent dose calculations and for maximizing the usefulness of data derived from animal safety and efficacy studies.

37. Development of Best Practices for Handling Missing Data. All clinical research studies experience some level of subject attrition, ranging from a few patients to more than half of the study subjects. When patients are lost to follow-up, an intent-to-treat analysis requires imputation of missing data. Depending on the extent of the imputation, the validity of the trial results can come into question, causing delays and possibly unnecessary failures. There is increasing dissatisfaction with one common approach, Last Observation Carried Forward (LOCF), and broad agreement that alternatives are needed. Evaluation of different analytical approaches (e.g., testing potential alternative to LOCF against existing data sets) and development of consensus on how to impute missing data in a variety of different situations would enhance efficiency of product development in nearly every therapeutic area.

38. Development of Trial Protocols for Specific Therapeutic Areas. Consensus on trial designs that

are tailored to specific diseases or conditions (e.g., how to select participants, structure of the trial, outcome and endpoint measures, duration) would facilitate development. For example, new clinical trial designs and end-points for age-related macular degeneration therapy trials could unleash innovation in this area of unmet medical need. Some suggest that it will be possible to develop a library of standard disease-specific trial protocols. For example, the assessment of drugs for their abuse liability is an important societal and development concern and requires the conduct of specific clinical trials. The available data need to be reviewed and discussed to develop guidance on the best ways to conduct those trials.

39. Analysis of Multiple Endpoints. In many diseases, more than a single efficacy endpoint may be of importance. Stakeholders are looking for clarification on appropriate statistical methods for handling multiple trial endpoints. Key issues include the statistical implications of requiring success on more than one endpoint, appropriate statistical adjustment when endpoints are correlated, and handling of secondary endpoints. Stakeholders are also looking for clarification of appropriate methods for sequential analyses of endpoints.

Improving Measurement of Patient Responses

40. Measuring Disease-Related Symptoms. For many diseases, it is possible to measure a variety of important indicators, but there are no rigorous or standard measures of disease symptoms. As a result, important information about patient response may be poorly captured and described. For example, standardized outcomes and endpoints are needed for symptomatic gastrointestinal disorders, psoriasis, and atopic dermatitis. Pain scores are needed for abdominal disease, irritable bowel syndrome, and endometriosis.

41. Measuring Patient-Centered Endpoints. Identifying endpoints of value to patients and integrating them into clinical trials would make trials more effective by improving the connection between trial results and clinical improvement. Today, however, it is often unclear which signs and symptoms matter most to patients and, in many cases, there are no standard agreed-upon scales to measure patients' preferred endpoints. This issue has been raised for diseases ranging from Parkinson's disease to COPD to lung cancer. More rigorous methods for determining and measuring patient priorities in clinical testing would provide more pertinent information than the broad measures of quality of life typically used today.

42. New Trial Design in Oncology. Most cancer trials identify and test the maximum tolerated dose, to maximize efficacy. Such trials cannot answer key questions about dose/response relationships: Do

blood levels of drug relate to outcomes? At what dose does the response plateau? Because survival is often their primary endpoint, cancer trials are not designed to identify potential response measures that change early in treatment. New trial designs that allow a better understanding of concentration response, as well as early indicators of response, could improve the safety of both cancer trials and cancer therapy.

43. Improving Efficacy Endpoints for Infectious Diseases. Typically, to determine whether an antibiotic or vaccine is effective against a particular pathogen, the presence or levels of the infectious agent in the patient are followed. However, the presence of a pathogen does not always correlate with illness, and the purpose of some vaccines is to arrest the disease process, rather than prevent infection or clear the infectious agent. For many infections, there is no consensus on what patterns of symptoms define the disease. Therefore, it is difficult to measure how an experimental product affects the disease. Consensus on what changes in symptoms could constitute a benefit in the treatment of infectious disease and how to measure them would significantly improve efficacy endpoints in clinical trials of agents that target certain infectious diseases. Similarly, studies of the natural history of specific infections could provide reliable data on the likely length of the infections to help sponsors design trials in which efficiency endpoints can be measured sooner.

Streamlining the Clinical Trial Process

44. Development of Data Standards. Currently, clinical investigators, clinical study personnel, data managers, and FDA reviewers must cope with a plethora of data formats and conventions. Some clinical investigators report the presence of many different computer systems for data entry at their sites (for various trials), each of which uses different data conventions. Lack of standardization is not only inefficient, it multiplies the potential for error. Important standards work is underway, but much

remains before the promise of shared data standards for clinical trials is realized. CDISC is paving the way by developing its Study Data Tabulation Model for describing observations in drug trials.¹ That model could someday encompass observations needed for other types of trials. Health Level 7 and CDISC are working to create standards that can be

¹ For more on CDISC (the Clinical Data Interchange Standards Consortium), see <http://www.cdisc.org/>.

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used for the exchange, management, and integration of electronic healthcare information to increase the effectiveness and efficiency of healthcare delivery.² In addition to improving and expanding the Model, sponsors and the FDA must undertake the hard work of retooling hardware and software to apply the new standards. This retooling includes training researchers to collect and FDA reviewers to expect data in these formats. Standardizing data archiving conventions would also enable the creation of shared data repositories, facilitating meta-analyses, data mining, and modeling to improve clinical trial design and analysis.

45. Consensus on Standards for Case Report Forms. Clinical trial data collection, analysis, and submission can be inefficient and unnecessarily expensive. A wide array of different forms and formats are used to collect clinical trial information, and most data are submitted to the FDA on paper. Differences in case report forms across sponsors and trials creates opportunities for confusion and error. Standardization of the look and feel of case report forms could reduce these inefficiencies and also help accelerate progress toward electronic data capture and submission.

² See also <http://www.hl7.org/>.

TOPIC 3: HARNESSING BIOINFORMATICS

Data Pooling and Simulation Models

46. Identification and Qualification of Safety Biomarkers. Collaborative efforts to pool and mine existing safety and toxicology data would create new sources for identification and qualification of safety biomarkers. For example, a robust database of preclinical and clinical data on cardiac arrhythmic risk could help us understand the clinical significance of QT interval prolongation, reduce the need for clinical studies, and, possibly, help identify individuals who are at risk for this side effect. Similarly, evidence-based simulation models of drug metabolism that correlate preclinical and clinical toxicity, and new criteria for use of such models, would enable sponsors to make smarter dose selection decisions for clinical trials and promote development of more predictive safety biomarkers.

47. Virtual Control Groups in Clinical Trials. Databases, models, and/or imaging collections could be used by multiple sponsors across different product types as historical controls to reduce the necessary size of control groups in clinical trials. This approach would be of particular benefit to product development for rare disorders when sponsors cannot find a large number of patients to study. These techniques would also be of special benefit in instances when use of placebos is infeasible or unethical. Trusted third parties could be used to hold data or images and create an open source library. For example, today it is impossible to test a new drug as monotherapy in epilepsy. Patients need to maintain existing therapies, so new therapies can only be studied in combination with existing drugs. Use of historical controls might enable sponsors to demonstrate effectiveness of a new drug as monotherapy if the data could be assembled and rigorously analyzed.

48. Adverse Event Data Mining. Combining adverse event data related to a product, a class of products, or a disease could enable identification of previously undetected patterns of safety events and/or

comorbidities and could elucidate drug-drug interactions. This knowledge could then be applied to investigational products to better avoid known safety pitfalls.

49. Multiple Complex Therapies. Pooled data on the effects of combined use of complex technologies—for example, multiple implanted devices, microwave therapy to coronary vessels followed by a stent, or radiation therapy in a person with an implanted device—would create information that would improve both patient safety and new product development.

50. Modeling Device Performance. A rigorous model of specific aspects of human physiology could allow more predictive in-silico (computer-based) testing of implanted devices, prior to human testing. Such models could also yield information about the likely long-term performance of implanted devices to identify problems that may occur beyond the time periods studied in clinical studies and could answer current questions about device failures. Simulation technologies that model the physiological environment and dynamic forces acting on an implanted device could also provide information to bridge gaps in knowledge when clinical testing is difficult, such as with pediatric populations. For example, computer modeling of pediatric cardiac physiology could streamline development of devices for this population.

51. Clinical Trial Simulation. Clinical trial simulation—using in silico modeling—can predict efficient designs for development programs that reduce the number of trials and patients, improve decisions on dosing, and increase informativeness. Clinical trial simulation requires the development of a disease model, with subsequent integration of information on the investigational product. Such models could also help refine some of the innovative trial designs described in Topic #2, above.

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Stakeholders are looking for first steps, such as identification of tools and best practices.

52. Failure Analysis. Development of a public database of information from trials of unsuccessful products could allow identification of patterns associated with failure and help sponsors avoid repeating past mistakes. Failure analysis is a routine and rigorous aspect of engineering and other applied sciences. Combining efforts to learn more about the causes of problems—using anonymized, safe harbor methods—would provide the best opportunity to create useful generalized knowledge.

53. Natural History Databases for Rare Diseases. Many rare diseases are hard to study due to both the difficulty in enrolling subjects and the long duration of clinical trials. Databases recording the natural history of patients with rare diseases, incorporating observations on clinical progression and biomarkers, could assist in creating disease models and better designing clinical programs and, possibly, contribute virtual historical control groups

TOPIC 4: MOVING MANUFACTURING INTO THE 21ST CENTURY

Manufacturing, Scale-up, and Quality Management

Manufacturing Biologics

54. Improving Manufacture of Influenza and Other Vaccines. The use of poultry eggs to produce influenza vaccine has been associated with a variety of public health problems, ranging from limitation on vaccine supply (due to the process needed to grow vaccine stock in eggs) to product contamination. A well-characterized and publicly available library or banks of cell lines certified to be free from adventitious agents, known to remain genetically stable, with documented low risk for tumorigenicity, and known to grow easily for scaled-up manufacture would resolve this key hurdle to innovation in development of cell-based influenza vaccines. Such a cell bank would also promote more efficient development of other biological products, including therapeutic protein products, gene therapy products, and other types of vaccines.

55. Characterizing Cell Therapies. Cell therapies hold tremendous promise for treating an array of conditions, ranging from heart muscle disorders to brain disease. To date, there are no cell therapy biomarkers that accurately establish the essential characteristics of cord blood stem cells used to treat cancer and radiation injury, pancreatic islet cells used to treat diabetes, and cardiac cells derived from stem cells for treatment of heart disease. Additionally, cell therapies present special safety concerns. For example, there is risk that the administered cells will migrate to the wrong tissue, or settle into the right tissue but over time develop into cancer cells. Scientific tools are needed to better characterize the cells to ensure that cell therapies will reliably travel to and stay in the appropriate tissue and will develop into normal healthy cells.

56. Novel Approaches to Characterizing and Standardizing Biological Products. New methods of measuring the physical characteristics of biological products, such as nuclear magnetic resonance, x-ray crystallography, and/or mass spectroscopy could be used to provide a link between the physical characteristics measured by these tests and the clinical outcomes. Today, these techniques remain underused, pending scientific and consensus development work to understand how physical characteristics predict the purity and performance of biological products.

57. Detecting Contamination in Biological Products. A significant scientific hurdle in developing biological products is contamination with undesirable infectious agents, because the product is developed from living organism sources that may harbor these pathogens. To demonstrate that the product is safe for human use, sponsors must be able to detect contamination from viruses, bacteria, and other organisms that are found in living organisms (e.g., the prion agent of *mad cow* disease). New microarray technologies hold promise for detecting contamination—deliberate or accidental—of biological products. But more work needs to be done in this important field.

58. Enabling Manufacturing Changes for Well-characterized Proteins. Currently, production scale-up can be a rate-limiting step in the development of investigational proteins. New tools are needed to predict and assess the effect of manufacturing changes on product performance and to assess comparability to product made using previous processes. Availability of such tools could improve

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development efficiency and early patient access to investigational proteins.

59. Tissue Engineering. A key hurdle holding back innovation in tissue engineering is the difficulty in sufficiently characterizing a finished product to enable development of meaningful quality controls and release specifications. Often, conventional techniques, such as simple cell morphology, used to evaluate cell characteristics cannot be applied to these products because, for example, the engineered

product may also include nonbiological materials (e.g. a support matrix). Consensus on how to assess these products and ensure manufacturing consistency would give product sponsors the predictability they need to unlock innovation in tissue engineering.

60. Vaccine Potency. Improved, more quantitative and reliable non-animal based tests of vaccine potency would assist in development of vaccines for conditions such as rabies and smallpox.

Manufacturing Devices

61. Device Interaction with Blood Flow. Better predictive modeling of the shearing forces and rate of thrombosis caused by implanted devices would enable innovation in physical design and materials.

62. Development of a Biocompatibility Database. A publicly accessible database of the biocompatibility profile of materials used in the design and manufacture of implanted medical devices would facilitate continuous improvement in design of these products.

Manufacturing Drugs

63. Identifying Safety Effects of Excipients. Inactive ingredients in drugs have been identified as the cause of safety problems and, in some cases, have stalled progress or caused product development to fail. Earlier studies of the safety effects of excipients would allow sponsors to identify problems before making significant investments in testing a particular formulation.

64. Manufacturing Novel Dosage Forms. Examples of novel dosage forms include patches, liposomes, topicals, and nasal and pulmonary inhalers. Such products are developed to target delivery of drugs, improve compliance and ease use for patients, and deliver drugs that are difficult to formulate. It can be difficult to assess the quality of a manufactured product. For example, extracting a drug from patch products for quality assurance analysis can cause changes in the product. Aerosol quality is affected by difficult-to-measure characteristics such as spray density. New methods and testing instruments for consistent manufacture of such products are needed. Similarly, existing analytical techniques are often not designed to assess the quantities or forms of drugs found in some drug-device combination products.

65. Developing Standards for Spectroscopic Instruments. A number of rapid, noncontact, nondestructive, data-rich analytical methods that are new to drug manufacture could be more widely used if accepted scientific standards to ensure proper operation of instrumentation were developed. For example, studies to identify appropriate instrument qualification and calibration standards for new techniques such as Raman and Terahertz spectroscopy—to specify both a suitable set of material samples along with a corresponding set of specifications determined by a common statistical procedure—could dramatically improve manufacturing quality and predictability.

Nanotechnology

66. Characterizing and Qualifying Nanotechnologies. Nanotechnology holds huge promise for the design and manufacture of many types of novel medical products—from devices to therapeutics to combination products. There remain, however, a number of questions about the behavior of nanoparticles and the potential effects of products containing nanoparticles once they are introduced into complex human physiology. We need to better

understand the physical and chemical characteristics of different nanomaterials, and we need new test methods, characterization protocols, and standards so sponsors can efficiently move nanoproducts from preclinical through clinical development, to commercialization.

TOPIC 5: DEVELOPING PRODUCTS TO ADDRESS URGENT PUBLIC HEALTH NEEDS

Rapid Pathogen Identification

67. Improving Anti-Microbial Product Testing. New scientific technologies hold the potential for developing rapid, point-of-care tests for pathogen identification. These technologies could also improve the speed and accuracy of resistance testing. Use of rapid diagnostic tests (either a single test or a panel of tests) could greatly improve the efficiency of clinical trials for infectious diseases.

68. Screening Donated Blood and Tissue. Research to adapt these new technologies for rapid pathogen identification would also facilitate the development of novel screening tests for biological products. Of particular interest in screening donated blood and tissue are technologies that can perform rapid analysis for multiple organisms, on smaller quantities of blood and tissues. In a public health emergency involving infectious agents, such screening tools would be a key bulwark against the risk of inadvertent or deliberate transmission of infection to recipients of donated blood and tissues.

Better Predictive Disease Models

69. Animal Models to Test Bioterrorism Countermeasures. Today, limited animal models exist for determining biological activity of anthrax lethal toxin, and those that are available have questionable relevance to the mechanism of action of this virulence factor in humans. A nonhuman primate model for testing the efficacy and safety of antibiotic treatments and vaccines against inhaled anthrax—the most likely route of exposure to this agent in the case of a bioterror attack—would facilitate development of such products. New animal models more appropriate to the human condition also are needed for smallpox infection, radiation injury, and SARS.

70. New Small Animal Models for Vaccine Testing. Developing new small animal models to replace current primate models would greatly facilitate the development of vaccines for potential

bioterror agents and emerging or re-emerging infectious disease (because many primate models are expensive and have not been qualified). Of particular interest are new small animal models that predict the neurotoxicity of vaccines.

71. New Tissue Models. Before a product is tested in animals, it is tested in living cells in the laboratory. A major hurdle facing the development and evaluation of vaccines for emerging viral diseases, such as West Nile virus, SARS CoV virus, and smallpox virus, is the lack of a tissue culture assay that quantitatively measures and reliably predicts the protective immune response to candidate vaccines. Similarly, better cell culture systems to study the hepatitis C virus are needed to improve progress toward a hepatitis C vaccine.

TOPIC 6: SPECIFIC AT-RISK POPULATIONS — PEDIATRICS

Unlocking Innovation in Pediatric Products

72. Better Extrapolation Methods and Best Practices in Pediatric Trial Design. Pediatric product testing often begins with extrapolating safety and efficacy data from adult experience to determine the dose and administration schedule to be tested. During the past several years, a substantial number of pediatric trials have been conducted using this approach. If the data from those trials could be compiled into a database for quantitative analysis, sponsors could exploit past experience to assess the accuracy of different methods of extrapolation and reveal the most effective methods. Analysis of such a database could reveal best practices for other aspects of pediatric trial designs as well, enabling sponsors to avoid repeating less useful or inefficient trial designs. As a result, fewer children would be exposed to unnecessary or suboptimal clinical studies.

73. Drug Metabolism and Therapeutic Response. It is likely that differences in drug metabolism among adolescents affect their responses to antidepressant drugs. With improved knowledge, sponsors could tailor drug doses being tested to the study participants according to their drug metabolic genotype. The hard work of identifying specific genetic polymorphisms and signals in children and teens that predict a heightened risk for adverse events or nonresponse to treatment is in the early stages. Improving dosing could reduce side effects and increase successful outcomes.

74. Diagnosing Depression Subtypes. Many scientists and clinicians believe that depression (including adolescent depression) is not a single disease, but a collection of several related but biologically distinguishable conditions. However, there has been little success in furthering our understanding of the genetic/physiologic basis of depression. Better clinical definitions of depressive subtypes, along with better tools for classifying individuals, should help in achieving the goal of

developing treatments targeted to the adolescent's particular syndrome. For example, advanced imaging techniques targeting neurotransmitter activity may be able to identify depressive subtypes. Unfortunately, the best first steps toward this mechanistic understanding of depression have yet to be identified.

75. Animal Models for Maternal Vaccines. In the first few weeks of life, infants may be exposed to respiratory syncytial virus, group beta hemolytic streptococcus, and *E. coli* bacteria. Even if a vaccine existed, several weeks are required post-vaccination to develop a protective response, leaving infants at risk during that time. One approach to this public health issue would be safe and effective maternal vaccination, in which the pregnant woman develops a protective antibody response that is transferred to the fetus through the placenta or to the infant through breast-feeding. Obvious fear of the risks of exposing a fetus to vaccines and the associated immune stimulation have limited development of such approaches. Development of animal models to evaluate the safety outcomes of maternal vaccination on infants could unlock innovation and eventually lead to products that reduce illness and death due to infant infections.

76. New Therapies for Juvenile Diabetes. Development of an artificial pancreas for children (and adults) with diabetes could be accelerated by creating new clinical protocols (based in part on reassessing clinical outcomes from prior research) and improved outcome measures for evaluating the performance of continuous glucose sensors and a closed loop artificial pancreas. This work could also revolutionize diabetes care and management.

L-18

REUSE OF SINGLE-USE DEVICES

Question. Last summer, Congress passed the Medical Device User Fee Stabilization Act to continue the medical device user fee program, adjust user fees, and tighten up branding provisions related to reprocessed devices.

How soon will FDA issue the final guidance related to reprocessed devices?

Answer. We hope to issue the final guidance shortly.

Question. Will the final guidance differ significantly from the current draft?

Answer. Because the guidance has not yet been finalized and cleared, we cannot say whether or not it will differ significantly from the current draft.

Question. Will the final guidance assure that reprocessed single-use devices are adequately marketed so reports of malfunctions and serious injuries are reported correctly during the entire time a particular device is being reprocessed or reused?

Answer. Yes. FDA believes that the final guidance will be adequate to ensure that reprocessed single-use devices are adequately marked to ensure that reports of malfunctions and serious injuries are reported correctly during the time a reprocessed device is used.

Question. Will the FDA ensure that the labels that meet the branding requirements actually make it in to the patient chart when used by a hospital?

Answer. FDA's primary task will be to ensure and monitor that reprocessed single use devices include the appropriate identification and labeling. The hospitals and other facilities that use these devices will have responsibility for ensuring that health care personnel attach labels to patient charts as appropriate. FDA intends to work with manufacturers, hospitals, and the Joint Commission for the Accreditation of Health Organizations to do outreach and encourage health care facilities to establish procedures to ensure that these labels are properly attached to patient charts.

Question. Recent media attention to the reprocessing of single use devices has raised many concerns about the practice. The original Medical Device User Fee and Modernization Act required the FDA to review the most commonly reprocessed devices. The FDA reviewed a small subset of reprocessed single use devices and nearly 50 percent of the reviewed devices were either withdrawn or were declared not-substantially-equivalent.

What is FDA doing to ensure patient safety is not compromised by the use of reprocessed single use devices? Can FDA do more to ensure patient safety is not compromised by the use of these reprocessed single use devices?

Answer. FDA implemented the new premarket requirements put into place by the Medical Device User Fee Act, or MDUFMA, for reprocessed single-use devices, also known as SUDs. Manufacturers who intend to reprocess certain types of SUDs must now submit premarket 510(k) notifications for these devices which contain validation data on cleaning, sterilization and functionality. The additional premarket requirements apply to reprocessed SUDs determined to be high risk for transmission of infection or inadequate function following reprocessing, involving those reprocessed SUDs intended to come into contact with tissue at high risk of being infected with the causative agents of brain-wasting Creutzfeldt-Jakob disease. The reprocessed SUDs that are subject to the additional premarket requirements noted include 21 device types that were previously exempt from premarket notification requirements, and 52 device types that were already subject to 510(k) premarket notification requirements, but were not previously required to submit validation data.

FDA's postmarket oversight of reprocessors of SUDs includes inspections of manufacturing operations and review of adverse event reports. Since August 2000, FDA has inspected 29 reprocessing companies and over 200 hospitals to ensure that the third party reprocessors are following quality system regulations and that any hospitals engaged in reprocessing are also in compliance with these manufacturing requirements. During that time period, FDA issued eight warning letters to third party reprocessors and obtained two injunctions against firms. FDA issued regulatory correspondence outlining violations to four hospitals but has found that most hospitals are no longer reprocessing SUDs. In fiscal year 2005, FDA inspected seven reprocessing companies and found all of them in substantial compliance with applicable regulations.

FDA continues to review adverse events submitted by manufactures, user facilities and the general public for problems associated with reprocessing of single use medical devices. FDA changed its MedWatch reporting forms to make it easier for device users to inform the agency when a reprocessed SUD is associated with an adverse event. In addition, FDA recently issued draft guidance to implement the provision of the Medical Device User Fee Stabilization Act, or MDUFSA, that requires reprocessors to ensure that each SUD clearly identifies the reprocessor. The new provision, which will go into effect in August 2006, is intended to facilitate accurate reporting of adverse events involving reprocessed SUDs.

FDA believes the measures Congress put into place for reprocessed single use devices under MDUFMA establish appropriate controls to provide reasonable assurance of safety and effectiveness for these devices. The controls, which include additional data requirements, premarket review, and labeling provisions, have supplemented the inspection and enforcement authorities FDA already had in place.

FDA DETAILEES

Question. Please provide information on the FDA detailees sent to work in the Congress over the past 10 years, including the office they work in at FDA, the office they were or are detailed to in the Congress, the length of service, and FDA's policy on providing detailees to the Congress.

Answer. I would be happy to provide that and the HHS Instruction 300-3, Detail of Employees for the record.
[The information follows:]

FDA DETAILEES

Name	FDA offices	Detail location	Length of detail
David Dorsey, J.D	Office of the Commissioner; Office of the Chief Counsel.	Senate Health, Education, Labor, and Pensions Com- mittee.	Jan. 2001-Present
Dr. Brian Harvey	Center for Drug Evaluation and Research Office of New Drugs.	White House, American Polit- ical Science Association Congressional Fellowship.	Oct. 2000-Oct. 2001
Stacy M. McBride	Office of the Commissioner; Office of Management.	Senate Appropriations Sub- committee.	April 2005-Nov. 2005
Dr. Kevin Mulry	Center for Devices and Radi- ological Health; Office of De- vice Evaluation.	Office of Senator Richard Dur- bin Office of Legislative Af- fairs.	Jan. 1998-Aug. 1998
Thomas B. O'Brien	Office of the Commissioner; Office of Management; Of- fice of Financial Manage- ment.	House Appropriations Com- mittee.	Feb. 2004-Nov. 2004 Jan. 2005-Feb. 2006
Dr. Donna-Bea Tillman	Center for Devices and Radi- ological Health; Office of De- vice Evaluation.	Congresswoman Louise Slaughter-New York.	Jan. 2000-July 2000
Lisa Siegel	Office of the Commissioner; Division of Budget Formu- lation and Presentation.	House Agriculture Appropria- tions Subcommittee.	Feb. 1999-Oct. 1999
Maureen Holohan	Office of the Commissioner; Office of Planning.	House Agriculture Appropria- tions Subcommittee.	Feb. 2000-Oct. 2000
Margaret Carlson	Center for Food Safety and Ap- plied Nutrition.	Senate Health, Education, Labor, and Pensions Com- mittee.	Mar. 2002-Jan. 2004
Dennis Strickland	Center for Biologics Evaluation and Research; Office of Communication, Training and Manufacturers Assis- tance.	Office of Senator William Frist (Brookings Legislative Fel- lows Program).	Jan. 1996-Dec. 1996
Tracy Summers	Center for Food Safety and Ap- plied Nutrition; Office of the Director.	Office of Senator Edward Ken- nedey FDA Desk.	Aug. 1999-Nov. 1999
Diane Prince	Office of the Commissioner; Office of Legislative Affairs.	House Energy and Commerce Subcommittee.	May 1998-Jul. 1998
Jeff Shuren	Office of the Commissioner; Office of Policy.	Senate HELP Committee Office of Senator Edward Ken- nedey's Office.	Nov. 1999-Nov. 2000
Theresa Mullin	Office of the Commissioner; Office of Planning.	Office of Senator Byron Dorgan	Mar. 2000-Aug. 2000
Dave Doleski	Center for Biologics Evaluation and Research; Manufactur- ers Branch II.	Office of Senator Paul Wellstone (Brookings Legis- lative Fellows Program).	Jun. 1999-Dec. 1999
Serina Vandegrift	Office of the Commissioner; Office of Policy.	Senate Agriculture Committee (Chairman Cochran).	Jan. 2004-Jan. 2005
Tim Lynagh	Office of the Commissioner; Office of Legislation.	Office of Congressman Chris Smith.	2003
Mike Skonieczny	Office of the Commissioner; Office of Legislation.	Office of Congresswoman Rosa DeLauro.	2001

HHS TRANSMITTAL 96.2

PERSONNEL MANUAL

Issue Date: 2/22/96

Material Transmitted.—HHS Instruction 300-3, Detail of Employees (pages 1-3)
Material Superseded.—HHS Instruction 300-3 (all).

Background.—This Instruction has been substantially streamlined in accordance with National Performance Review recommendations, and in support of HHS administrative initiatives calling for more streamlined rules and greater delegations of authority.

Any reference to “OPDIV” in this Instruction now includes the PHS agencies, the Office of the Secretary, the Program Support Center, HCFA, ACF, and AOA.

This issuance is effective immediately. Implementation under this issuance must be carried out in accordance with applicable laws, regulations, and bargaining agreements.

Filing Instructions.—Remove superseded material and file new material. Post receipt of this transmittal to the HHS Check List of Transmittals and file this transmittal in sequential order after the check list.

JOHN J. CALLAHAN,

Assistant Secretary for Management and Budget.

INSTRUCTION 300–3

DISTRIBUTION: MS (PERS): HRFC–001

HHS PERSONNEL INSTRUCTION 300–3

DELEGATION OF AUTHORITY TO DETAIL EMPLOYEES

A. Authority Delegated

1. Heads of Operating Divisions (including PHS agencies and the Program Support Center), the Assistant Secretary for Management and Budget for the Office of the Secretary (OS), and the Inspector General (for OIG) are delegated the authority to:

- a. detail and extend details of civil service personnel within the Department in increments not to exceed 120 days, pursuant to 5 U.S.C. 3341; and
- b. detail and extend details of civil service personnel to or from other Federal organizations on either a reimbursable or a non-reimbursable basis pursuant to 31 U.S.C. 1535.

2. These authorities may be redelegate with further redelegation authorized.

B. Restrictions

1. The term “Federal organizations” in paragraph A.1.b. above does not include the Executive Office of the President and the Legislative and Judicial Branches of Government.

2. The Assistant Secretary for Management and Budget retains the authority to approve all details to or from the Executive Office of the President and to or from the Legislative and Judicial Branches of Government (including the General Accounting Office, the Library of Congress, and the Government Printing Office).

C. Exclusions

1. This delegation does not cover:

- a. Assignments of excepted employees other than those with Schedule A and B or VRA appointments to competitive service position (5 CFR 6.5);
- b. Details of Administrative Law Judges (5 U.S.C. 3344);
- c. Details to certain Executive positions (5 U.S.C. 3344–3349) ;
- d. Details of members of the Senior Executive Service (5 CFR 317.903) ;
- e. Details of PHS Commissioned Officers (42 U.S.C. 215);
- f. Details between HHS and a non-Federal organization under Section 214 of the PHS Act, as amended;
- g. Details under the Intergovernmental Personnel Act of 1970 (5 U.S.C. 3372–3374; and 5 CFR Part 334); and
- h. Details to an International organization (5 U.S.C. 3343; and 5 CFR 352.304).

D. Information and Guidance

1. The authorities delegated in paragraphs A.1.a and b. above must be exercised in accordance with the requirements and/or provisions in the following references:

- a. U.S.C. 112 (Details to the Executive Office of the President)
- b. U.S.C. 3341 (Details within Executive or Military Departments)
- c. Civil Service Rule 5 CFR 6.5 (Assignment of Excepted Employees)
- d. 31 U.S.C. 1301 (Appropriation Restrictions on Assignment of Employees)
- e. 31 U.S.C. 1535 (Assignment of Employees Between Executive Branch Departments and Agencies and Written Agreements Between Agencies Detailing Employees)
- f. 4 CG 848–849, April 13, 1925 (Appropriations and Transfer)
- g. 21 CG 954, April 27, 1942 (Details to the Legislative Branch)

- h. 21 CG 1055, May 26, 1942 (Details to the Legislative Branch)
- i. 64 CG 370, B-211373, March 20, 1985 (Nonreimbursable Details)

E. Prior Delegations

This delegation supersedes the February 19, 1991, Delegation of Authority to Detail Personnel, as amended September 29, 1993, from the Assistant Secretary for Personnel Administration to the Heads of Operating Divisions and Regional Directors. To the extent that previous redelegations of the authority to detail personnel made to other officials within HHS are consistent with the provisions of this delegation, they may remain in effect until new redelegations are made under the authority of this delegation.

F. Effective Date

This delegation is effective on the date of this transmittal.

BSE—FEED BAN

Question. Yesterday afternoon, USDA announced that the third cow in United States history tested positive for BSE, commonly known as mad cow disease.

The FDA feed-ban rule, issued in 1997, is the first line of defense in preventing BSE infection in U.S. cattle.

What is FDA doing to ensure that it is inspecting all entities that are subject to the feed ban?

Answer. FDA inspects a wide variety of firms in the animal feed industry to confirm compliance with the ruminant feed ban regulation. Every firm that manufactures, processes, blends, transports, or distributes animal feed or feed ingredients for any animal species is subject to inspection under the FDA ruminant feed ban compliance program. Firms are subject to inspection under the FDA ruminant feed ban regardless of whether prohibited material is used or the relative risk the firms practices may pose to the U.S. BSE feed control program. In addition to feed manufacturers and distributors, over one million farm operations feeding ruminants such as dairy and beef cattle are subject to the rule.

The BSE Ruminant Feed Inspection Compliance Program guidance document constitutes the FDA risk-based inspection priority approach used by FDA and state investigators. FDA gives highest priority to inspecting firms that manufacture or process animal feeds or feed ingredients that contain prohibited material. This industry segment of renderers, protein blenders, and feed mills are inspected annually to ensure that ruminant feeds do not contain prohibited materials.

FDA also conducts inspections on firms considered to have a reduced risk producing or causing contamination of ruminant feed. The agency conducts inspections of these lower risk firms to detect overall compliance trends. If FDA detects compliance trends, agency staff implements more targeted inspectional initiatives to increase our presence in some of these lower risk industry segments.

PANDEMIC INFLUENZA

Question. How is FDA using the \$20 million for pandemic influenza provided in the fiscal year 2006 supplemental?

Answer. The \$20 million supplemental was received at the end of the first quarter and the funds were available on January 26, 2006. I would be happy to provide the spending plan for the record.

[The information follows:]

Food and Drug Administration Pandemic Influenza Request (Dollars in Millions)			
Pandemic Flu Vaccine Capacity	President's Proposed FY 2006 Supplemental	FTE	Description of Activities
CBER – Enhance regulatory science base to facilitate new vaccines.....	16.7	75	Expand FDA capacity to facilitate the expedited development, evaluation and licensure of additional flu vaccines and manufacturing capabilities and capacity to meet pandemic preparedness needs, consistent with the DHHS Pandemic Influenza Strategic Plan. This includes developing and assessing new technologies, assuring the safety and effectiveness of vaccines, serving as consultants on product development and inspecting manufacturing facilities.
Office of Regulatory Affairs – Post medical products/vaccines approval inspections.....	1.2	7	Experienced investigators will conduct bioresearch monitoring, drug manufacturer and flu vaccine manufacturer inspections, to assure product quality and prevent problems that threaten product safety or availability early in the development cycle. The requested resources will also allow ORA to expand current efforts to identify and intercept counterfeit products either claiming to prevent the flu or treat its symptoms.
Other Activities (OC) – Office of Crisis Management/Office of Counterterrorism Policy.....	0.8	3	Support additional duties associated with strategic planning, policy leadership, coordination and communication of the FDA's pandemic influenza activities and design an agency-specific response to the threat of pandemic, consistent with the DHHS Pandemic Flu plan.
Other Activities (OM) – IT/Systems Requirements.....	1.2	0	Modifications to IT Systems to ensure that critical information is available during the product life cycle.
Total FDA Request.....	20.0	85	

Question. How does FDA plan to use the \$30.5 million requested in fiscal year 2007?

Answer. I would be happy to provide that information for the record.
[The information follows:]

Food and Drug Administration Pandemic Preparedness Request (Dollars in Millions)		
Pandemic Flu	FY 2007 Request	FTE
Biologics - Enhance regulatory science base to facilitate new vaccines.....	5.9	38
Biologics - Develop virus reference strains for manufacturing.....	8.9	20
Field - Medical product manufacturing inspections and compliance activities.....	0.04	0
Other Activities (OC) - Office of Crisis Management/Office of Counterterrorism Policy/Office of Management.....	0.2	0
Animal and Human Health and Food Issues		
Foods - Research and communication on foodborne transmission of virus.....	4.2	7
Foods - Validate and implement methods to detect H5N1 virus.....	1.6	5
Animals - Antiviral residues in poultry.....	0.8	1
OCM, Field - Emergency response and quarantine planning.....	1.6	6
Foods, Animals, Field, OCTPP - Biosecurity measures.....	2.3	2
Foods, Field - Surveillance.....	3.1	0
Drugs - Anti-Virus.....	1.0	5
Drugs, OCTPP - Rapid Response.....	0.7	3
Total FDA Request.....	30.4	85.0

Description of Activities	
Expand FDA capacity to facilitate the expedited development, evaluation and licensure of additional flu vaccines and manufacturing capabilities and capacity to meet pandemic preparedness needs. This includes the development of new technologies assessing the safety and effectiveness of vaccines, serving as consultants on product development and inspecting manufacturing facilities.	
Prepare a library of pandemic influenza virus high growth reassortants (seed strains) suitable for manufacturing and using the latest and emerging technology, including reverse genetics, assure that seed strains are available for large scale manufacturing, test and approve manufacturers seed viruses for new strains, and prepare strain specific reagents and achieving harmonized international standards for use by manufacturers to assure vaccine potency and quality.	
Experienced investigators will conduct bioscience monitoring, drug manufacturer and flu vaccine manufacturer inspections, to assure product quality and prevent problems that threaten product safety or availability early in the development cycle. The requested resources will also allow OCM to expand its capacity to identify and intercept counterfeit products either claiming to prevent the flu or treat its symptoms.	
Support additional offices associated with strategic planning, policy leadership, coordination and information management. This includes the DHS Pandemic Flu team. Modifications to information systems to ensure that critical safety and effectiveness information is available during the product life cycle.	
Conduct research on possible foodborne transmission of the pandemic influenza virus and equine field trials and support technology transfer and training of field scientists to ensure adequate capacity to respond to outbreaks of avian influenza	
Validate new and modified methods to detect foodborne H5N1 virus	
Develop and validate methods to detect antiviral products in poultry and coordinate with USDA on sampling and testing imported poultry products for traces of antiviral residues.	
Develop and implement plans for containment and disposal of animal liver that has or may have been contaminated with avian flu agents and will develop, integrate and execute FDA animal and food response plans and quarantine activities, in coordination with USDA and CDC.	
Develop best practices on biosecurity measures for the rendering, food and feed industries. Consult with industry, state government agencies and other stakeholders on biosecurity strategy.	
Improve its capacity to conduct domestic and import surveillance and report to reports of food or feed contamination associated with viruses to support national pandemic influenza surveillance integration efforts.	
Enhance manufacturing processes for bioscience products, to improve production efficiency. Develop methods of collection and evaluating product safety information in a pandemic setting. Assemble rapid response teams to support accelerated development of medical countermeasures for pandemic and to address other pandemic related issues requiring expedited Agency input or resolution.	

IMPORT INSPECTION

Question. FDA plays a significant role in import inspection at ports. For example, FDA inspects food, human drugs, animal feeds, and medical devices at ports of entry across the country.

For FDA-regulated food products, FDA estimates that by 2007 the amount that comes across the border will have nearly quadrupled since 1999. In a typical year, FDA physically examines less than 1 percent of these food imports. How does FDA keep up with the ever increasing amount of imported products?

Answer. FDA attempts to keep up with the increasing volume of imported products by using a risk based approach when selecting shipments to inspect and sample. All products are screened electronically by FDA's Operational and Administrative System for Import Support, also known as OASIS, against a set of criteria established as a result of previous laboratory findings, foreign inspections, information received from other regulatory agencies, and the relative risks posed by the products in question.

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 requires anyone intending to import or offer for import a food product must provide prior notice to the FDA before the shipment arrives at the border. Every Prior Notice submission is screened electronically. If specific criteria are met, FDA's Prior Notice Center will review those submissions using various intelligence targeting parameters to protect the Nation's food supply against terrorist acts and other public health emergencies. For example, currently, working with information submitted through Customs and Border Protection's electronic systems used for import entries or through FDA's internet-based Prior Notice System Interface, FDA screens shipments electronically before they arrive in the United States to determine if the shipments meets identified criteria for physical examination or sampling and analysis or warrants other review by FDA personnel. This electronic screening allows FDA to better determine how to deploy our limited physical inspection resources at the border on what appear to be higher-risk food shipments while allowing lower-risk shipments to be processed in accordance with traditional import procedures after the electronic screening.

Question. Does FDA have adequate resources to properly inspect imports?

Answer. The rapid growth of imports combined with ever present security concerns has increased the need to assess the status of imported products. FDA estimates it will review more than 19 million import lines for admissibility into domestic commerce in fiscal year 2007. To help ensure the safety of imported products entering the United States, FDA electronically screens imports through the Operational and Administrative System for Import Support, also known as OASIS. OASIS is an automated system for processing and making admissibility determinations for FDA regulated products that are offered for import. FDA also performs laboratory analysis on products offered for import into the United States; conducts foreign inspections to evaluate manufacturing conditions of products before they are offered for import; and performs periodic filer evaluations to ensure that the import data being provided to FDA is accurate.

The Prior Notice Center, also known as PNC, is another important part of FDA's import strategy. The mission of FDA's PNC is to identify imported food and feed products that may be intentionally contaminated with biological, chemical or radiological agents, or which may pose significant health risks to the American public, and intercept them before they enter the United States. FDA will continue to focus resources on Intensive Prior Notice Import Security Reviews of products that pose the highest potential bioterrorism risks. The PNC uses a combination of adaptable targeting strategies and weighted risk indicators in the threat assessment process including contemporary intelligence involving terrorist activities, a history of prior notice violations, and compliance with admissibility standards as indicated by the results of import field exams, filer evaluations, firm inspections, repeated prior notice violations, and feedback from Field Investigators. By using a risk based approach, the PNC can intercept potentially hazardous products before they enter the United States.

The benefit of these reviews comes from the quality and targeting of review activities; not from the volume of imports inspected. Thus the quality of import screening is a better measure of FDA's import strategy rather than simply focusing on the items physically examined.

DRUG SAFETY

Question. Drug safety is a topic that has been very much in the news over the past year, and in your written testimony, you discuss the challenges the agency

faces in balancing the need for proper risk analysis while trying to speed the review process.

This subcommittee has closely followed FDA's drug safety activities. Last year, we provided an increase of \$10 million for drug safety. This amount was \$5 million more than the budget request. In fiscal year 2007, FDA is requesting an additional \$3.9 million for drug safety.

How is FDA using the \$10 million increase we provided last year?

Answer. In its fiscal year 2006 budget submission to Congress, FDA requested a base increase of \$5 million to bolster the drug safety functions performed within the Center for Drug Evaluation and Research's Office of Drug Safety, also known as ODS. These included three important increases. First, ODS will increase the professional staff in ODS who manage and lead safety reviews. Second, ODS will increase the number of staff with expertise in critical areas, such as risk management, risk communication, and epidemiology. Third, ODS will expand our information technology infrastructure for monitoring post-marketing data by increasing access to a wide range of clinical, pharmacy, and administrative databases. Valuable information regarding the safety of drug products is available in these types of databases for use by our scientists in ODS.

The approval by Congress of the Administration's fiscal year 2006 request for a \$5 million increase significantly strengthens the ability to conduct drug safety activities within ODS.

Congress increased our \$5 million request to \$10 million, adding to our original request an additional \$5 million for general drug safety program activities. The Center for Drug Evaluation and Research will use these funds to increase its emphasis on effective risk communication. The additional funds will further enable FDA to modernize its drug safety program and expand the understanding of, involvement in, and access to, external population-based and "linked" databases, such as the CMS Medicare and Medicaid databases. Accessing these databases represent the future of more thorough and continued monitoring of drug products after they are marketed. Information obtained from these databases, combined with voluntarily reported adverse event information, will substantially increase the agency's ability to efficiently and effectively identify, investigate, and notify consumers of possible drug safety concerns and take appropriate regulatory actions. FDA will also continue its efforts to improve the Adverse Event Reporting System, also known as AERS, so the agency can more efficiently review medication error reports and more quickly take appropriate action to avert further medication errors.

These funds will also allow FDA to hire additional expert staff across the Center to enhance the ability to use multidisciplinary, multi-office teams to analyze and interpret drug safety data before and after product approval. FDA plans to hire additional scientists to address its highest priority safety needs, such as responding to emerging drug safety issues, supporting FDA's Drug Safety Oversight Board, and increasing resources devoted to risk assessment and communication activities. These funds will also assist Center efforts to ensure that drug safety information is available to healthcare professionals, patients, and other consumers.

Question. What will the additional \$3.9 million allow FDA to accomplish in fiscal year 2007?

Answer. FDA requested additional funds in fiscal year 2007 to continue to modernize its AERS system 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. With more than 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.

Beyond the modernization of the AERS system, however, we requested these funds because 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. These include databases maintained by organizations such as the Center for Medicare and Medicaid Services, the Department of Veterans Affairs, the Department of Defense, and the Indian Health Service. We will also access clinical and hospital and pharmacy networks and insurers, such as health maintenance organizations, preferred provider organizations, 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. The planned modernizations for AERS are expected to optimize internal access and review of adverse event.

HUMAN TISSUE SAFETY

Question. In February of this year, FDA ordered a New Jersey human tissue recovery firm to cease operation because it found that the company had seriously violated FDA regulations governing donor screening and record keeping practices. FDA inspection and action followed a news article that uncovered the fact that this company was regularly and illegally harvesting human tissues from funeral homes. These tissues were subsequently transplanted into dozens of patients.

What is FDA doing to make sure situations like this do not happen again?

Answer. FDA wishes to clarify information regarding this matter. As part of an audit consistent with FDA regulations, a tissue processor in Florida noticed discrepancies in records supplied to it by the New Jersey tissue recovery firm. The Florida firm then took the following steps: initiated a recall of tissue it had processed and distributed, quarantined tissue it still had in its possession, and notified FDA. FDA began an inspection of the New Jersey firm in October, 2005, and found that the firm had failed to comply with regulations designed to prevent the spread of communicable diseases. Tissues harvested by the New Jersey firm had been sold to several processors and subsequently transplanted.

FDA is committed to establishing and maintaining high standards for tissue safety and to detecting, investigating and taking enforcement action against violations of its regulatory requirements. FDA continues to evaluate its tissue regulations and policies on an ongoing basis.

Question. Is there a certification or licensing procedure that tissue processing firms must go through before they can begin operating?

Answer. FDA regulations require that tissue processing establishments register with FDA and list their products within 5 days after beginning operations. FDA's District Offices use these registrations to schedule inspections to assure compliance with the regulations designed to promote patient safety and to prevent the spread of communicable diseases.

Question. Does FDA regularly inspect human tissue firms?

Answer. FDA performed 270 inspections of human tissue establishments in fiscal year 2005. The Agency anticipates it will perform 250 inspections in fiscal year 2006 and 325 inspections in fiscal year 2007. FDA is in the process of implementing its new risk-based approach to assure the safety of human cells, tissues, and cellular and tissue-based products, or HCT/Ps. The Agency is using a comprehensive approach for regulating existing and new cell and tissue products. FDA is in the process of addressing issues related to safety and effectiveness of a rapidly growing industry.

A rule expanding the types of tissue facilities required to register with the FDA and list their HCT/Ps became effective January 21, 2004. The donor eligibility rule became effective May 25, 2005, and focuses on donor screening and testing measures to prevent the transmission of communicable diseases from the donor through HCT/Ps. The current good tissue practice rule also became effective May 25, 2005. This rule requires manufacturers to recover, process, store, label, package and distribute HCT/Ps in a way that prevents the introduction, transmission, or spread of communicable diseases. These rules are critical new tools that give FDA the ability to monitor human tissue adverse reactions to target more effectively the products with the highest risks.

PROPOSED USER FEES

Question. FDA is proposing two new user fees in the budget request. One will require manufacturers to pay for the full cost of follow-up inspections when FDA must revisit facilities because of initial bad inspection reports. The second fee would reimburse FDA for the cost of issuing export certificates for food and animal feeds.

Can you explain why you believe these fees are necessary?

Answer. Although FDA issues export certifications for all products it regulates, the agency only has authority to charge a fee to issue export certifications for human and animal drugs, and medical devices. Timely issuance of food and feed export certificates funded through user fees would improve the ability of food and animal feed producers to export their products and would eliminate the current preferential treatment of the food and feed industry differences in authority to collect fees for the food and feed industries.

FDA conducts post-market inspections of food, human drug, biologic, animal drug and feed, and medical device manufacturers—both domestic and foreign—to assess their compliance with Current Good Manufacturing Practice, or CGMP, and other FDA requirements. In 2004, approximately 1,500 out of 21,000 firms inspected were found non-compliant with CGMPs and other important FDA requirements. Under current law, FDA does not have the authority to assess fees for any follow-up inspections conducted by FDA to ensure that manufacturers have addressed violations that were found during the previous inspection. A fee for repeat inspections will serve as an incentive to industry to conform to CGMPs and other FDA requirements and will ensure that the financial burden of re-inspections is more equitably shared between industry and the public.

Both fees are designed to improve the overall management of these activities.

Question. Has FDA sought input from impacted organizations?

Answer. Discussions with industry have not yet been held.

Question. Have you submitted the text of your legislative proposal to the authorizing committee?

Answer. The legislative proposals are in the final stages of review. We expect the proposals will be submitted to the Congress within the next several weeks.

Question. Please explain the services FDA will be reimbursed for by the re-inspection user fee.

Answer. If a firm undertakes corrective action to achieve compliance, FDA will verify the appropriateness and completeness of the corrective action. For the firm to satisfy FDA's concerns and, if regulatory action was taken, to resume its full ability to market products, the firm must be reinspected by FDA and found in compliance.

These user fees will provide funding to FDA to act in a timely manner to ensure that noncompliant firms have taken appropriate corrective action and to facilitate the return of compliant firms to full marketing of violative products. Some of the activities that FDA performs in conducting reinspections include the scheduling and preparatory reinspection work by the FDA investigator, the reinspection itself, sample analyses, report writing, compliance officer review and analysis, conferring with experts, and travel and administrative time.

Question. Please explain the services FDA will be reimbursed for by the food and animal feed certification fee.

Answer. The services FDA will be reimbursed for by the food and animal feed certification fee include: reviewing applications and attestations; checking of field and headquarters administrative records, and with personnel for the compliance status of the firm; review of the product label for compliance with the law; preparing, processing, and issuing of the certifications, including notarization; maintenance of applications and copies for tracking of services rendered and for provision of certificate copies when requested; all other clerical procedures necessary to issue the certifications within 20 days including processing of billing and receipts, and other costs attributable to the issuance of certifications. Currently certifications are processed on an "as resources permits" basis.

FOOD DEFENSE

Question. Over the past 5 years, this subcommittee has provided more than \$600 million for food defense activities at FDA. The fiscal year 2007 budget requests an increase of \$19.8 million for food defense activities. This is a significant investment.

How has FDA used the funding we have provided to make the food supply safer?

Answer. FDA uses the food defense funding to build upon the Nation's core food safety and public health systems and to strengthen our capabilities to address terrorist threats. FDA's efforts to protect the food supply focus primarily on six major crosscutting initiatives under Homeland Security Presidential Directive-9, also known as HSPD-9, for food defense.

One example of FDA's HSPD-9 activities is the establishment of the Food Emergency Response Network, a national network also known as FERN, to increase analytic surge capacity in the event of terrorist attack by developing adequate laboratory testing capacity for biological, chemical and radiological agents in food. The Agency continues to develop FERN by providing laboratory infrastructure, training, and proficiency testing to member laboratories. FDA is conducting targeted food defense research efforts, including prevention technologies, methods development, determination of infectious dose for certain agents when ingested with food, and agent characteristics within specified foods. Also, FDA is performing more effective targeted risk-based inspections using data from FDA's Prior-Notice system and Prior Notice Import Security Reviews based on intelligence, FDA inspection reports, discrepancies in prior notice reporting, and sample collection and analysis. As part of

the government-wide Biosurveillance Initiative, FDA is improving coordination and integration of existing food surveillance capabilities with the Department of Homeland Security's integration and analysis function. FDA is upgrading and expanding its Emergency Operations Network Incident Management System to assist in the management and coordination of the Agency's response to incidents affecting the U.S. food supply. Along with the U.S. Department of Agriculture, the Federal Bureau of Investigation, and Department of Homeland Security, FDA began a new collaborative effort with States and private industry to protect the Nation's food supply from terrorist threats through the Strategic Partnership Program Agroterrorism Initiative. FDA has spearheaded this effort to identify sector-wide vulnerabilities, mitigation strategies, and research needs to protect our Nation's food supply.

Question. Does FDA have an overall plan for food defense, including out-year costs? Can you provide this information for the record?

Answer. FDA's overall plan for food defense aligns with the activities outlined in Homeland Security Presidential Directive-9 also known as HSPD-9, which establishes a national policy to defend the food and agriculture system. The directive lays out a framework for augmenting the Nation's food safety protections by identifying and prioritizing sector-critical infrastructure and key resources for establishing protection requirements, developing awareness and early warning capabilities to recognize threats, mitigating vulnerabilities at critical production and processing nodes, enhancing screening procedures for domestic and imported products, and enhancing response and recovery procedures.

With regard to future activities, the fiscal year 2007 requested funds will be used to expand the Food Emergency Response Network, also known as FERN, to include 16 State laboratories, provide grants and technical support to these laboratories, and build analytic surge capacity to respond to a terrorist attack. We will also use these funds to manage, through the National Program Office, the network and to provide training and proficiency testing for FERN laboratories. We will continue Field support for food defense operations, including targeting potentially high-risk imported foods through Prior Notice Import Security Reviews based on intelligence, FDA inspection reports, discrepancies in prior notice reporting, and sample collection and analysis.

FDA also will continue laboratory preparedness efforts and valuable short-term food defense research projects. Many of the projects undertaken are derived from direct interaction with industry following vulnerability assessments. The results of these projects can be communicated directly to industry. These efforts will result in a better understanding of which interventions work, and which do not, for certain agents in specific foods.

In addition, the fiscal year 2007 requested funds will further joint food defense and food safety assignments that will enhance and facilitate the integration of food defense with food safety. In these assignments, samples obtained as part of routine food safety programs will also be tested in a variety of laboratories for a range of select agents that are of most concern. The foods chosen for these assignments are generally foods that we have most concern about based on vulnerability assessments.

Out-year activities will further strengthen our food defense system and advance the objectives identified in HSPD-9.

DRUG EFFICACY STUDY IMPLEMENTATION (DESI) MONOGRAPH SYSTEM

Question. In response to Senate Committee Report language accompanying the fiscal year 2005 agriculture appropriations bill, FDA prepared a report on the feasibility of developing a drug monograph system for older prescription drugs that have been marketed for a material extent and material amount of time without documented safety problems. In this report, FDA stated that a monograph system would be scientifically infeasible and cost prohibitive. However, FDA did not propose an alternate solution to this monograph system.

The Senate Committee Report to accompany the fiscal year 2006 Agriculture appropriations bill requested a second report asking FDA to propose an alternate approach that provides for the uniform and transparent regulation of these products.

What is the status of this report?

Answer. FDA is working on this report and hopes to submit it to Congress this summer.

Question. Has FDA developed an alternate method as requested in the report language?

Answer. The agency is working on its approach to the regulation of these products and plans to discuss alternatives in our report to the subcommittee.

MEDICAL IMAGING DRUGS

Question. Since FDA terminated the Medical Imaging Drugs Advisory Committee in 2002, FDA has tried to fill the gap in medical imaging expertise by retaining experts as special government employees and appointing them on an ad hoc basis to meetings of a standing advisory committee when a medical imaging product or issue needs advisory committee review. I understand that at the last advisory committee meeting to consider a medical imaging product, which was held in March 2005, FDA appointed three medical imaging drug experts to a standing panel of 17 experts. In light of the increasingly important role of medical imaging drugs and medical imaging biomarkers under FDA's Critical Path initiative, I am interested in FDA's ability to get the necessary medical imaging expertise on these panels. How many medical imaging experts has FDA retained as special government employees?

Answer. Currently, FDA has a list of 89 special government employees, or SGEs, with medical imaging expertise who may be requested to participate in regulatory activities, including FDA drug advisory committee and device panel discussions. The 89 SGEs includes 72 members of various Medical Devices Advisory Committees and consultants. These SGEs are also accessible for drug review consultation.

Question. What is FDA doing to improve the recruitment of medical imaging experts as special government employees? Are there any barriers to such recruitment?

Answer. The ability of a special governmental employee, or SGE, to assist in FDA activities varies considerably, based predominantly upon competing SGE commitments and timelines. Hence, FDA is actively recruiting additional SGEs via interactions with professional societies and visiting professor lecture activities. Barriers to SGE recruitment relate to conflict of interest considerations and the limited reimbursements to SGEs.

Question. How many medical imaging expert special government employees does FDA intend to hire in the future?

Answer. FDA is currently processing materials for 12 medical imaging experts as potential special government employees. When vacancies are imminent on Medical Devices Advisory Committees, FDA requests professional society assistance in obtaining voluntary applicants.

COLOR CERTIFICATION

Question. The fiscal year 2007 budget request includes an increase in current law user fees of \$180,000 for the Color Certification Program. Please explain this increase.

Answer. As in previous years, FDA estimates that an increase of 3 percent in poundage will be submitted for color certification in fiscal year 2007 over fiscal year 2006. This will generate an estimated \$180,000 in additional color certification revenue and is not related to any rate increase for the Color Certification Program.

Question. In April 2005, FDA increased the color certification fee through an interim final rule, with no opportunity for comment from industry. FDA has stated this was necessary in order to ensure that the fund was not depleted. At the same time, FDA stressed the need to keep adequate reserves in order to ensure adequate levels of funding. Given that FDA has worked to ensure an adequate reserve fund, would it be possible for FDA to seek public comment in advance of any future color certification fee increase?

Answer. Historically, solicitation of public comment has not been deemed a prerequisite for increasing color certification fees. As required under the Federal Food, Drug, and Cosmetic Act, also known as the FD&C Act, Section 721(e), the fees assessed for color certification reflect those costs necessary to provide, maintain, and equip an adequate service for such purposes. Section 721(e) does not provide for notice-and-comment rulemaking for assessing or increasing fees. Since passage of the 1938 FD&C Act, FDA increased the color certification fees several times, most recently in 1963, 1982, 1994 and 2005. FDA stated, in the March 29, 2005 interim final rule, that the fee modification is necessary because of a general increase in all costs of operating the certification program. In the interim final rule, FDA found under 5 U.S.C. 553(b)(B) and 21 CFR 10.40(e) that providing for public comment before establishing the fees, and for revising the basis for calculating the fees, is contrary to the public interest. Despite this finding, the agency stated in the interim final rule that it invited and would consider public comments on the requirements in the rule. The interim final rule became effective on April 28, 2005, and FDA requested comments by May 31, 2005. Comments, as well as a request for a stay of the effective date and a citizen petition, were submitted to the docket and are under consideration.

Question. Has FDA taken any steps to make the color certification fees and program expenses more transparent?

Answer. FDA's Office of Financial Management, also known as OFM, occasionally submits certification fund updates to industry representatives; this information is always provided to industry representatives upon request. OFM maintains detailed accounting records of color certification expenditures and other related non-proprietary information. These statements include expenditure reports, status of funds reports, and projected yearly estimates for the various allowances within the Color Certification program.

Question. Please provide a list of anticipated equipment needs, including estimated costs, necessary to maintain adequate service for certification of batches of color additives.

Answer. I would be happy to provide that information for the record.
[The information follows:]

COLOR CERTIFICATION PROGRAM—ANTICIPATED EQUIPMENT NEEDS AND RELATED COSTS—
FISCAL YEAR 2007-FISCAL YEAR 2009

Item	Description	Estimated Cost (per three years)
Maintenance contract for computer database.	Certification operating system and web-based industry interface.	\$300,000
Maintenance contracts for large equipment.	High-performance liquid chromatographs (approximately 21 systems).	250,000
	Liquid chromatograph/mass selective detector	25,000
	X-ray fluorescence spectrometer	60,000
	Atomic absorption spectrometer	30,000
	Ion chromatograph	16,500
	Microwave digestion and ashing systems	15,000
Replacement parts for equipment	X-ray fluorescence spectrometer (x-ray tubes, sample changer parts, helium/vacuum switch).	75,000
	Atomic absorption spectrometer (furnace tubes, lamps)	30,000
	Microwave digestion and ashing systems (parts, crucibles)	7,500
	Shatterbox (grinding tools)	5,000
	Pellet press (press tools)	2,500
Anticipated new large equipment	High-performance liquid chromatographs (expect to purchase two annually).	460,000
	X-ray fluorescence spectrometer	350,000
	Liquid chromatograph/mass selective detector	120,000
	Ion chromatograph	10,000
	Preparative high-performance liquid chromatograph	45,000
	Flash preparative chromatograph	25,000
	Automatic titrator	17,000
	Microwave ashing system	20,000
	Fusion machine and platinum ware	50,000
	Freeze drier	15,000
	Microwave synthesizer	20,000
	Uninterruptible power supply	30,000
	Reaction system	20,000
Anticipated new small equipment	Analytical balances (5), top-loading balances, lab computers, spectrophotometers, fluorescence detector, moisture analyzer, centrifuge rotor, digital camera.	250,000
Hazardous waste disposal	Disposal of chemical waste	300,000
Stockroom contract	Reagents, glassware, misc. lab supplies	330,000
Misc. purchases	Computer software, reagents, misc. lab supplies	400,000
Total		3,278,500

Question. What is the anticipated timeframe for these equipment needs?

Answer. Certification requirements are assessed in 3 year cycles. FDA's anticipated timeframe for these equipment needs is 3 years.

FOOD CONTACT SUBSTANCES

Question. Since its implementation 6 years ago, the Food Contact Notification program has been successful. I understand that the Food Contact Notification program requires less FDA resources than the previously used Food Additive Petition process because the FCN program does not require the Agency to follow Notice and Comment Procedures and promulgate a new regulation. In addition, the clearance of a

new material under the Food Additive Petition program typically took 2 to 4 years, but the Notification program only takes 4 months. The success of the program has led to the clearance of over 500 new types of packaging materials.

If the FCN program is more efficient, why would FDA seek to eliminate the program and return to promulgating regulations, and how does FDA plan to accomplish its statutory mandate under the food additive petition process when it does not seek to add additional resources to handle these submissions?

Answer. The Food Contact Notification, also known as FCN, program has been very successful. Under the FCN program, if FDA does not object within the 120-day review period, a company can legally market its product. To date, FDA has always met the 120-day deadline. In contrast, under the Food Additive Petition, also known as FAP, program, the petitioned food contact substance cannot lawfully be marketed until a regulation is published by FDA. Reverting to the FAP process for food contact substances will not have an adverse impact on the public health because these substances cannot be marketed until FDA completes a full safety review of each substance. Prior to the implementation of the FCN program, FDA had implemented many changes to the FAP process and had made significant progress in streamlining the review of food additive petitions. Although FDA does not expect to be able to meet its statutory mandate of publishing a decision on a petition within 180 days of filing, we will continue our efforts to streamline the petition review process and to reach decisions in a timely manner.

Question. What is FDA's assessment of the impact that the elimination of the FCN program will have on packaging innovation and on public health?

Answer. Elimination of the FCN program will not have a significant adverse impact on the public health because pre-market approval of food contact substances will still be required and food contact substances will still have to meet the same safety standard so that unsafe food contact substances do not reach the market. As in the past, petitions in which the subject additive is intended to have an impact on the public health, for example reducing pathogens on food, will be prioritized and expedited through the review and administrative process. Thus any impact on public health will be minimal.

NEW DRUG APPLICATIONS

Question. On February 13, 2006, the Justice Department, on behalf of FDA, represented to the U.S. District Court for the District of Columbia that the Omnitrope New Drug Application, which was submitted in fiscal year 2003, is still undergoing active review by the Agency. However, in the FDA's fiscal year 2007 budget submission the Agency reported that, for NDA submissions during fiscal year 2003, which would include this application, FDA reviewed and acted on "100 percent of 82" fiscal year 2003 NDA submissions by the end of fiscal year 2004. Please explain this apparent discrepancy. Was action completed on all NDAs or are there submissions from fiscal year 2003 still under review?

Answer. As FDA described in an August 2004 letter to the sponsor of the Omnitrope NDA, the reviewing division had completed its review of the information in the NDA. However, because the agency was considering related scientific and legal issues in its review of pending citizen petitions, and scientific considerations related to the approval of products like Omnitrope were to be the subject of a series of public meetings, FDA was not ready to make an approval decision on the application. The agency deferred a decision on the Omnitrope NDA until the agency knew whether the data in the NDA was sufficient for approval and, if not, what additional substantive information and data might be necessary to support approval. The letter identified what additional steps had to be completed before the agency could inform the sponsor of the actions necessary to place the Omnitrope NDA in condition for approval. Therefore, it was considered an action in accordance with the PDUFA performance goals. All fiscal year 2003 NDA submissions have been completed and final performance has been reported.

SUNSCREEN MONOGRAPHS

Question. The statement of managers accompanying the fiscal year 2006 conference report directed FDA to issue a comprehensive final monograph for labeling over-the-counter sunscreen products, including UVA and UVB labeling requirements, by May 10, 2006. Please describe the status of FDA's efforts or plans to finalize the sunscreen labeling guidelines by this deadline.

Answer. We are currently working on a rulemaking for OTC sunscreen drug products to address both UVA and UVB labeling requirements. We are currently working to publish the document for this rulemaking in the Federal Register.

QUESTIONS SUBMITTED BY SENATOR MITCH MCCONNELL

NATIONAL INSTITUTE FOR PHARMACEUTICAL TECHNOLOGY AND EDUCATION

Question. In June 2005 the Center for Drug Evaluation and Research's Office of Pharmaceutical Science within the Food and Drug Administration (FDA) signed a Memorandum of Agreement with the National Institute for Pharmaceutical Technology and Education (NIPTE). The University of Kentucky (UK) is a member of NIPTE.

As the FDA considers funding priorities for fiscal year 2007, I am interested in answers to the following questions raised by NIPTE and UK.

The Memorandum of Agreement expresses the FDA's desire to collaborate with NIPTE on issues related to pharmaceutical development, manufacturing practices and technologies.

To date, what interaction has the FDA had with NIPTE?

Answer. FDA has had some preliminary discussions with NIPTE about issues of mutual interest. NIPTE has expressed concerns about the level of products failing during development.

Question. NIPTE has concerns that product failure during development is often related to the transition from a laboratory prototype to final product. They have expressed concerns that the limited amount of research into these failures causes production technology to lag behind efforts to discover new compounds.

Do you anticipate that the relationship between FDA and NIPTE will promote a more efficient therapy development and production process and if so, how?

Answer. It is not possible to determine, at this time, the outcome of any interactions with NIPTE. FDA works with many academic institutions and other interested parties on pharmaceutical development and manufacturing research to support FDA policy relating to Process Analytical Technologies product applications.

Question. The FDA's stated goal of the Critical Path to New Medical Products initiative is to modernize the scientific process through which drugs and other treatments are transformed from "proof of concept" into medical products.

How can the FDA take advantage of the infrastructure and resources of NIPTE's member institutions to promote the goals of the Critical Path initiative?

Answer. We expect the new manufacturing science created through CDER's contract with NIPTE to promote manufacturing process improvements as part of the Critical Path Initiative. It is not possible to determine, at this time, whether FDA can take further advantage of infrastructure and resources at NIPTE. FDA believes that the best way to advance the goals of Critical Path is to stimulate broad-based efforts that advance the goals of this initiative.

QUESTIONS SUBMITTED BY SENATOR SAM BROWNBACK

CLINICAL TRIALS

Question. I understand the FDA has regulatory authority to utilize a number of various controls to determine efficacy in the clinical trials process, which include the use of historical controls and placebo controls.

Is the FDA considering increasing the frequency of approval for study designs involving historical controls or even Bayesian statistics?

Answer. FDA is actively considering, under its critical path initiative, a variety of study designs, methods of analysis, and uses of data from other studies to improve decision making and the rate of success of studies. Although FDA does not approve study designs, we do discuss with sponsors whether we are likely to consider a particular design as representing an adequate and well-controlled study that could support approval under the Federal Food, Drug, and Cosmetic Act. The appropriate use and applicability of historical controls in which treatment of a group of patients is compared to well-documented experience from other studies is considered in detail in the ICH guidance E-10 known as the Choice of Control Group and Related Issues in Clinical Trials. FDA's regulations at 21 CFR 314.126, state that historical controls can be an acceptable kind of "adequate and well-controlled study," but only in special circumstances, such as studies of diseases with high and predictable mortality. Such controls are regularly used now, for example, in accelerated approvals of anti-cancer drugs based on tumor response rates. See 21 CFR 314.500. It is possible, and is worth studying, particularly for rare diseases, that better documentation of the natural history of diseases will provide a basis for wider use of historically controlled trials. With regard to medical devices, FDA's regulations at 21 CFR 860.7, allow for a wide variety of valid scientific evidence for premarket approval applications, including historical controls, where appropriate.

FDA has viewed Bayesian approaches as an alternative method in the design and evaluation of clinical studies. The frequency of use of such an approach is related to the medical product itself, the sponsor, the target population, and many other factors. Although FDA would consider the use of Bayesian statistics, few drug sponsors propose such designs. In May 2004, in an effort to emphasize our willingness to examine such designs, FDA and Johns Hopkins University jointly sponsored a very well-attended workshop for industry, academia, and government entitled, "Can Bayesian Approaches to Studying New Treatments Improve Regulatory Decision-Making?" The Center for Devices and Radiological Health has accepted designs involving Bayesian statistics since 1998, and there has been an increase in the frequency of investigational device exemptions that use Bayesian design and plan appropriate analyses.

Question. Please list the number of cancer drugs for which the FDA approved a study design that included a placebo-controlled trial, over the past 4 year period.

Answer. FDA does not "approve" study designs or protocols. Companies generally develop an overall drug development strategy, including specific protocols, to seek registration or approval in multiple countries such as the European Union, Japan, Switzerland, Canada, and Australia. FDA reviews, but does not approve these protocols.

In cancer settings, the term placebo-controlled is a misnomer. It is very rare for a cancer patient to only receive a placebo. Whenever possible, FDA encourages use of another available therapy as an active-control rather than a placebo. In situations where an active-control study cannot be conducted, FDA seeks to ensure that all patients receive best supportive care in addition to the test-article or placebo to which they are randomized.

Question. Please describe the process by which a cancer patient who has exhausted all other treatment options can gain access to a drug that has shown efficacy in an earlier stage of the clinical trials process.

Answer. The FDA has a long-standing commitment to desperately ill patients, including patients with cancer, to facilitate the availability of promising new drugs during the drug development process, when promising drugs are being studied, but are not yet approved for marketing. FDA's statute and regulations enable a patient suffering from a serious or immediately life threatening disease for whom no comparable or satisfactory alternative drug or other therapy is available to get access to a promising investigational drug. FDA is developing regulations to further clarify and publicize the expanded access mechanisms for such treatment use of investigational new drugs, in the belief that such new regulations will increase the awareness of and participation in expanded access programs. However, it should be noted that FDA does not have authority to compel a sponsor to make an investigational new drug available for treatment use.

In December 2003, FDA submitted to Congress its report on Patient Access to New Therapeutic Agents for Pediatric Cancer. This report includes how patients can access investigational drugs under current rules. I would be happy to provide for the record, the section of the report that describes our current system.

[The information follows:]

EXISTING PROGRAMS

Access Outside of Clinical Trials

It is not always possible for all patients who want access to investigational drugs to enroll in clinical trials. Patients may not meet eligibility criteria or may be geographically isolated from a study site. It may be difficult to find an ongoing trial for a particular type and stage of cancer. In these situations, FDA and NCI believe that it is appropriate to help make certain promising, but as yet unproven, products available outside of a clinical trial (non-protocol) to patients with cancer as well as other serious and life-threatening illnesses. Non-protocol investigational therapy should be offered in a way that does not pose an unreasonable risk to the patient or an unreasonable risk of losing valuable information about the effect of the drug. For these reasons, although treatment is focused on the individual patient, a study plan (protocol) may be written to ensure that the treatment is administered appropriately and that patients are monitored for toxicity. The programs available through both agencies are discussed below. It is important to note that a pharmaceutical manufacturer must first agree to provide the requested product for a non-protocol investigational therapy to begin. NCI and FDA cannot mandate that the requested products be supplied to these programs; the agencies can only review and approve proposals to use them.

FDA Programs for Non-protocol Access

FDA programs that permit non-protocol access to investigational agents for patients with serious or life-threatening disease include the single patient IND, the emergency IND, and the Treatment IND (sometimes informally referred to as an expanded access protocol). The lay public frequently refers to these programs as compassionate use, although the term compassionate use does not appear in FDA regulations. Single patient or emergency INDs refer to a treatment program for a single individual. Treatment IND refers to a single study plan used to treat multiple patients.

Single Patient IND Submissions

Single-patient IND submissions can represent entirely new uses for a drug or exceptions to an ongoing clinical trial protocol for a patient who does not meet protocol entry criteria. Single patient IND requests can be submitted as amendments to an existing IND or as an entirely new IND. They can be submitted by a drug manufacturer (usually amending an existing IND) or by an individual physician, following usual procedures for IND filing, including IRB review and informed consent. If the need for treatment is urgent and does not allow time for submission of an IND, an emergency IND can be obtained allowing FDA to authorize shipment of a drug for the specified use before the IND is submitted (21 CFR 312.36). The IND should then be submitted as soon as possible after receiving authorization. As with all INDs, both mechanisms require adverse event reporting and an annual summary to be submitted to FDA.

Treatment IND

Treatment IND study plans “facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and obtain additional data on the drug’s safety and effectiveness” (21 CFR 312.34). Certain criteria must be met for a drug to be considered for approval in a Treatment IND,¹ including:

- The patients’ disease must be serious or life-threatening.
 - No comparable or satisfactory treatment is available to the target population of patients.
 - The drug is in clinical trials (generally Phase 3 and not ordinarily prior to Phase 2).
 - The sponsor of the clinical trials is actively pursuing marketing of the drug.
- FDA may refuse the request if:
- For a serious disease, sufficient evidence of safety and potential efficacy is not provided to support use of the drug to treat it.
 - For a life-threatening disease, available scientific evidence does not provide a reasonable basis for concluding that the drug may be effective and would not expose patients to serious additional risk of illness or injury.

The same safeguards and reporting requirements that apply to any IND study apply to a Treatment IND, including IRB approval. The study plan must contain a rationale for the use of the investigational drug, as well as a list of what available regimens should be tried prior to its use, or an explanation of why the use of the investigational drug is preferable to the use of available marketed treatments.

NCI Programs for Non-protocol Access

At NCI, Special Exception and Group C protocols provide access to investigational agents for those patients unable to participate in a clinical trial.

Special Exception

The Special Exception is comparable to the single patient IND, but investigators may obtain investigational agents directly from NCI using NCI’s Special Exception mechanism instead of filing a new IND with FDA. NCI does not grant these requests for drugs in Phase 1 development, because NCI requires some demonstration of efficacy before permitting individual treatment. The written policy for this program requires objective evidence that the investigational agent is active in the disease for which the request is being made.

Anecdotal reports or reports that show low response rates or responses of brief duration are not sufficient to justify approval of the request. Patients must be ineligible for ongoing research protocols and must have received standard therapies.

Group C

Group C designation is an expanded access program similar to a Treatment IND that allows broadened access to investigational agents with reproducible activity in one or more specific tumor types. An agent must alter or be likely to alter the pattern of treatment of the disease, and properly trained physicians without specialized

supportive care facilities must be able to administer the agent safely. For an agent that meets this definition, CTEP may submit a formal application to FDA to authorize distribution of the agent (Group C distribution) by NCI for the specific indication described in the application. This application is not a marketing application, and FDA approval of a Group C protocol does not replace an FDA conclusion that the drug is safe and effective. The study plan must contain the indication, dosage, precautions, warnings, known adverse events of the product, and an informed consent form. Approval of the Group C protocol carries the obligation of the usual safety reporting requirements. This mechanism is used only with agents for which activity is sufficiently established and for which a New Drug Application (NDA) or Biological Licensing Application (BLA) approval is considered likely in the relatively near future.

QUESTIONS SUBMITTED BY SENATOR HERB KOHL

FIELD STAFF

Question. We discussed earlier the decrease in FDA field force, and I was told that this was a result of the streamlining of the FDA inspection process, and would not result in fewer, or less effective, inspections.

Please provide specific numbers of inspections that are scheduled to take place by all FDA field staff members in fiscal year 2007. Please organize these into the types of inspections FDA performs—for example, inspections of feed manufacturers, ports, food manufacturers, drug companies, overseas companies, etc. How do each of these numbers compare to fiscal year 2006 and 2005 levels?

Answer. I will be happy to provide a table that lists activities, by type of inspections, for fiscal years 2005, 2006, and 2007 for the record. Traditionally, that information is captured in a table entitled, “Combined Field Activities—ORA Program Activity Data” that appears in the published fiscal year 2007 FDA Congressional Justification, pages 272–277.

[That information follows:]

COMBINED FIELD ACTIVITIES—ORA PROGRAM ACTIVITY DATA

	Fiscal year 2005 actual	Fiscal year 2006 estimate	Fiscal year 2007 estimate
FOODS FIELD			
Program Outputs—Domestic Inspections:			
Domestic Food Safety Program Inspections	4,573	3,400	3,400
Imported and Domestic Cheese Program Inspections	477	400	400
Domestic Low Acid Canned Foods/Acidified Foods Inspections	481	400	400
Domestic Fish & Fishery Products (HACCP) Inspections	2,467	2,480	2,480
Import (Seafood Program Including HACCP) Inspections	500	500	500
Juice HACCP Inspection Program (HACCP)	490	375	375
Interstate Travel Sanitation (ITS) Inspections	1,510	1,700	1,700
State Contract Food Safety (Non HACCP) Inspections	6,992	8,130	8,130
State Contract Domestic Seafood HACCP Inspections	953	1,135	1,135
State Contract Juice HACCP	35	35	
State Partnership Inspections	1,284	1,300	1,300
Total Above FDA and State Contract Inspections	19,774	19,855	19,855
Total Domestic Reinspections (Non-add)	523	523	523
State Contract and Grant Foods Funding	\$6,825,000	\$7,100,000	\$6,940,000
Number of FERN State Laboratories	8	10	16
Annual FERN State Cooperative Agreements/Operations	\$12,270,000	\$7,037,000	\$12,236,000
Total State & Annual FERN Funding	\$19,095,000	\$14,137,000	\$19,176,000
Domestic Field Exams/Tests	3,528	5,000	5,000
Domestic Laboratory Samples Analyzed	15,390	11,425	9,425
All Foreign Inspections	129	200	100
Total Foreign Reinspections (Non-add)	15	15	15

COMBINED FIELD ACTIVITIES—ORA PROGRAM ACTIVITY DATA—Continued

	Fiscal year 2005 actual	Fiscal year 2006 estimate	Fiscal year 2007 estimate
Import Field Exams/Tests	84,997	75,000	71,000
Import Laboratory Samples Analyzed	25,549	31,600	29,600
Import Physical Exam Subtotal	110,546	106,600	100,600
Import Line Decisions	8,672,168	10,059,715	11,669,269
Percent of Import Lines Physically Examined	1.27	1.06	0.86
Prior Notice Security Import Reviews (Bioterrorism Act mandate) ..	86,187	45,000	60,000
COSMETICS FIELD			
Program Outputs—Domestic Inspections:			
All Inspections	138	100	100
Total Domestic Reinspections (Non-add)	7	7	7
Program Outputs—Import/Foreign Inspections:			
Import Field Exams/Tests	1,983	2,000	2,000
Import Laboratory Samples Analyzed	241	200	200
Import Physical Exam Subtotal	2,224	2,200	2,200
Import Line Decisions	1,146,049	1,398,180	1,705,779
Percent of Import Lines Physically Examined	0.19	0.16	0.13
DRUGS FIELD			
Program Outputs—Domestic Inspections:			
Pre-Approval Inspections (NDA)	149	130	130
Pre-Approval Inspections (ANDA)	81	135	135
Bioresearch Monitoring Program Inspections	562	520	520
Drug Processing (GMP) Program Inspections	1,365	1,500	1,440
Compressed Medical Gas Manufacturers Inspections	125	155	150
Adverse Drug Events Project Inspections	106	135	135
OTC Monograph Project Inspections and Health Fraud Project In- spections ¹	53	11	45
State Partnership Inspections: Compressed Medical Gas Manufac- turers Inspections	85	110	110
State Partnership Inspections: GMP Inspections	57	50	50
Total Above FDA and State Partnership Inspections	2,594	2,780	2,715
Total Domestic Reinspections (Non-add)	220	220	220
Domestic Laboratory Samples Analyzed	1,446	1,735	1,600
Programs Outputs—Import/Foreign Inspections:			
Foreign Pre-Approval Inspections (NDA)	163	180	180
Foreign Pre-Approval Inspections (ANDA)	77	60	60
Foreign Bioresearch Monitoring Program Inspections	85	65	65
Foreign Drug Processing (GMP) Program Inspections	217	195	195
Foreign Adverse Drug Events Project Inspections	10	25	25
Total Above Foreign FDA Inspections	52	525	525
Total Foreign Reinspections (Non-add)	17	17	17
Import Field Exams/Tests	4,288	4,400	4,400
Import Laboratory Samples Analyzed	1,045	355	300
Import Physical Exam Subtotal	5,333	4,755	4,700
Import Line Decisions	264,559	317,471	380,965
Percent of Import Lines Physically Examined	2.01	1.50	1.23

COMBINED FIELD ACTIVITIES—ORA PROGRAM ACTIVITY DATA—Continued

	Fiscal year 2005 actual	Fiscal year 2006 estimate	Fiscal year 2007 estimate
BIOLOGICS FIELD			
Program Outputs—Domestic Inspections:			
Bioresearch Monitoring Program Inspections	121	156	156
Blood Bank Inspections	1,439	1,130	1,070
Source Plasma Inspections	188	165	160
Pre-License, Pre-Approval (Pre-Market) Inspections	3	10	10
GMP Inspections	42	36	36
GMP (Device) Inspections	14	35	35
Human Tissue Inspections	270	250	325
Total Above Domestic Inspections	2,077	1,782	1,792
Total Domestic Reinspections (Non-add)	50	50	50
Program Outputs—Import/Foreign Inspections:			
Blood Bank Inspections	16	24	24
Pre-License Inspections	6		
GMP Inspections	15	24	17
Total Above Foreign FDA Inspections	37	48	41
Total Foreign Reinspections (Non-add)	4	4	4
Import Field Exams/Tests 1	143	100	100
Import Line Decisions	39,979	44,377	49,258
Percent of Import Lines Physically Examined	0.36	0.23	0.20
ANIMAL DRUGS & FEEDS FIELD			
Program Outputs—Domestic Inspections			
Pre-Approval/BIMO Inspections	72	140	110
Drug Process and New ADF Program Inspections	230	210	210
BSE Inspections	3,025	3,760	3,760
Feed Contaminant Inspections	3	15	15
Illegal Tissue Residue Program Inspections	203	245	245
Feed Manufacturing Program Inspections	369	240	40
State Contract Inspections: BSE	3,309	4,562	4,562
State Contract Inspections: Feed Manufacturers	457	347	347
State Contract Inspections: Illegal Tissue Residue	370	750	600
State Partnership Inspections: BSE and Other	988	900	900
Total Above FDA and State Contract Inspections	9,036	11,169	10,789
Total Domestic Reinspections (Non-add)	173	173	173
State Animal Drugs/Feeds Funding	\$1,300,000	\$1,700,600	\$1,800,000
BSE Grant Increase	\$3,000,000	\$3,000,000	\$3,000,000
State Contract for Tissue Residue	\$220,000	\$220,000	\$210,000
Total State Funding	\$4,520,000	\$4,920,600	\$5,010,000
Domestic Laboratory Samples Analyzed	1,841	1,770	1,730
Programs Outputs—Import/Foreign Inspections:			
Foreign Pre-Approval/Bioresearch Monitoring Program Inspections	26	45	45
Foreign Drug Processing and New ADF Program Inspections	12	10	10
Total Above Foreign FDA Inspections	38	55	55
Total Foreign Reinspections (Non-add)	3	3	3
Import Field Exams/Tests	4,298	4,500	4,500

COMBINED FIELD ACTIVITIES—ORA PROGRAM ACTIVITY DATA—Continued

	Fiscal year 2005 actual	Fiscal year 2006 estimate	Fiscal year 2007 estimate
Import Laboratory Samples Analyzed	753	1,120	900
Import Physical Exam Subtotal	5,051	5,620	5,400
Import Line Decisions	212,254	235,602	261,518
Percent of Import Lines Physically Examined	2.38	2.39	2.06
DEVICES FIELD			
Programs Outputs—Domestic Inspections:			
Bioresearch Monitoring Program Inspections	329	300	300
Pre-Approval Inspections	64	130	130
Post-Market Audit Inspections	63	65	65
GMP Inspections (Levels I, II, III and Accredited Persons)	1,430	1,530	1,530
Total Above Domestic Inspections: Non MQSA	1,886	2,025	2,025
Inspections (MQSA) FDA Domestic (non-VHA)	366	335	371
Inspections (MQSA) FDA Domestic (VHA)	32	32	32
Inspections (MQSA) by State Contract	8,340	7,924	7,700
Inspections (MQSA) by State non-Contract	545	530	530
Total Above Domestic Inspections: MQSA	9,283	8,821	8,633
Total Domestic Reinspections (Non-add)	237	237	237
State Contract Devices Funding	\$1,350,000	\$250,000	\$275,000
State Contract Mammography Funding	\$9,800,000	\$9,200,000	\$9,940,000
Total State Funding	\$11,150,000	\$9,450,000	\$10,215,000
Domestic Radiological Health Inspections	107	130	130
Domestic Field Exams/Tests	944	1,215	1,215
Domestic Laboratory Samples Analyzed	200	217	217
Programs Outputs—Import/Foreign Inspections:			
Foreign Bioresearch Monitoring Inspections	6	10	10
Foreign Pre-Approval Inspections	17	34	34
Foreign Post-Market Audit Inspections	26	27	27
Foreign GMP Inspections	225	207	189
Foreign MQSA Inspections	16	15	15
Foreign Radiological Health Inspections	9	19	19
Total Above Foreign FDA Inspections	299	312	294
Total Foreign Reinspections (Non-add)	24	24	24
Import Field Exams/Tests	6,901	5,000	5,000
Import Laboratory Samples Analyzed	1,333	1,440	1,440
Import Physical Exam Subtotal	8,234	6,440	6,440
Import Line Decisions	3,484,393	4,460,023	5,708,829
Percent of Import Lines Physically Examined	0.24	0.14	0.11

¹ The OTC Monograph and Health Fraud Inspections will no longer be planned separately in fiscal year 2006.

AVIAN FLU

Question. Is there any vaccine currently available that would protect humans from the H5N1 flu virus? How much? Please include experimental and approved, and explain the difference, and how the distribution would occur.

Answer. There is currently no FDA-approved vaccine available to protect humans from the H5N1 influenza virus that currently is circulating in Asia and parts of Europe. However, candidate H5N1 vaccines are in development.

In 2004, the National Institute of Allergy and Infectious Diseases, or NIAID, awarded two contracts for the production and clinical testing of H5N1 vaccines based on an H5N1 reference strain produced through reverse genetics. These vaccines are currently under evaluation in clinical trials, under protocols developed with FDA input. We have stated that, if provided adequate data, we would be able to approve a pandemic influenza strain that is used in an existing licensed vaccine process, in an expedited manner and without requiring a new license. Therefore, as the results of these studies are submitted to us by licensed manufacturers, we will be able to consider them rapidly for approval as supplements to existing vaccine licenses. Currently, unlicensed vaccines made with new technologies or with the addition of adjuvants to stimulate the immune response would require more extensive evaluation by FDA as new products. However, we are providing accelerated development and evaluation pathways to help assure the safety and immunogenicity of new influenza vaccines as efficiently and rapidly as possible.

To help manufacturers develop pandemic and seasonal influenza vaccines, we recently issued two draft guidances. These guidances provide recommendations on developing the information needed to show safety and effectiveness for new vaccines and outline expedited pathways to licensure. Among the issues discussed in the guidances are the use of new technologies, such as cell culture, recombinant technologies, and the use of adjuvants, in vaccine development and production.

To facilitate the availability of pandemic influenza vaccines prior to their licensure, if needed in an emergency, FDA could evaluate the benefit/risk ratio of pandemic influenza vaccines and, where appropriate, make such vaccines available under other regulatory mechanisms, including investigational new drug or Emergency Use Authorizations. With regard to vaccine distribution, the Department of Health and Human Services, or HHS, has announced procurement for the Strategic National Stockpile, also known as SNS, which includes vaccines that could be distributed for use in the event of a potential influenza pandemic. HHS provides oversight of the SNS, including responsibility for procurement and maintenance of vaccines and other medical products to be used in the event of an influenza pandemic or other public health emergency. FDA's role is to provide technical assistance and support for HHS efforts regarding the development, procurement, maintenance, and deployment of pandemic influenza countermeasures and other medical products held in the SNS.

After consultation with HHS, FDA offers the following information on the status of HHS efforts to support the stockpiling and distribution of candidate pandemic vaccines. Based on the latest scientific research, which indicates that two 90 microgram doses of the pre-pandemic H5N1 vaccine will be effective as a course of vaccination, HHS has ordered approximately 4 million courses of the vaccine. Of the 4 million courses, approximately 3.75 million courses have been manufactured, with the remaining courses on order. These courses are not being held in the Strategic National Stockpile; rather, they are being stored in bulk at cGMP-compliant storage facilities of the vaccine manufacturers awaiting instructions for formulation and fill finish into final containers. HHS will review clinical results from studies this summer which may indicate that adding adjuvant to the H5N1 vaccine may boost immune response to those who receive the vaccination. Once these results have been obtained and all doses are formulated and filled accordingly, they may be distributed to critical workforce groups as needed. Currently plans are for the H5N1 vaccine to reside with the vendor or vaccine manufacturer until deployment.

Question. Please summarize the FDA's ability, and timeframe necessary, in order to mass-produce vaccines for a human strain of H5N1?

Answer. FDA is actively engaged in facilitating the efforts of DHHS, manufacturers and other partners to develop and make available influenza vaccines, including those for the currently circulating H5N1 strain. While FDA can rapidly evaluate and approve the use of a new vaccine strain by a licensed manufacturer, and a new vaccine could start to become available within 4 months of its identification, current U.S. influenza vaccine manufacturing and the available technologies that support it are not adequate to quickly produce enough pandemic vaccine for the U.S. population. Therefore, we are aggressively supporting multiple efforts to increase manufacturing capacity using both new and existing technologies, including antigen sparing vaccines using both aluminum and novel adjuvants, which is a nonspecific simulators of immune response, as well as live attenuated vaccines, and cell-culture based and recombinant vaccines, which involves combining DNA from two or more sources. FDA scientists work with manufacturers throughout the year to collect information on the capability of new influenza viruses to be used for large-scale pro-

duction of influenza virus vaccines and to provide needed reagents and technical assistance. FDA has initiated annual inspections of licensed influenza vaccine manufacturers to help ensure that manufacturers are in compliance with good manufacturing practices, and to identify and, where possible, prevent problems ahead of time, and thus are able to manufacture safe and effective pandemic influenza vaccines in emergent circumstances.

Increasing the Agency's capacity to facilitate rapid evaluation, product testing, licensure, and production of vaccines is critical to expanding product availability, assuring timely and expert evaluation of product quality, supporting national preparedness and response capacities for pandemic influenza, and achieving public confidence in vaccine products. The funds requested for fiscal year 2007 are critical to achieving our goal of supporting a process whereby manufacturers can produce pandemic influenza vaccine in the shortest possible time to protect the greatest number of people, using a vaccine that is safe, effective, and easy to deliver.

With regard to vaccine production issues, we will use fiscal year 2007 requested funds to facilitate HHS and manufacturers' efforts to increase domestic manufacturing capacity to meet HHS goals, including a stockpile with enough vaccine to vaccinate 20 million people. FDA is supporting the longer term goals of HHS, manufacturers, and other partners to achieve pandemic surge production capacity that would make it possible to provide licensed vaccine for the entire U.S. population within 6 months of a strain being isolated, using a combination of current egg-based and, potentially, new high-volume, rapid response cell-based production. How quickly these goals can be met will in part be dependent on the results of current industry vaccine development programs, mostly assisted by HHS, including ongoing studies of adjuvanted and cell culture vaccines. In 2005, we were able to very rapidly facilitate the evaluation and U.S. licensure of an additional annual influenza vaccine, using our accelerated approval process, helping avoid major shortages. We will continue to do everything possible to facilitate both the process of vaccine development and the enhancement of manufacturing capacity, and Congress' support is critical in assuring FDA's capacity to both prepare for and respond to a pandemic.

Question. The budget proposes over \$55 million for pandemic flu preparedness. The very earliest this funding would be available is October 1, but we are hearing reports that the virus could arrive here in the United States, at least in birds, and potentially in humans, prior to that.

Do you believe we can afford to wait until the fiscal year 2007 bill to make this money available to FDA? If so, why? Would you support adding the additional funding to the pending supplemental in order to make it available more quickly?

Answer. Thank you for the opportunity to discuss the funding of FDA's Pandemic Preparedness activities. We appreciate your interest in supporting the FDA efforts in this initiative. The President's budget requests in fiscal year 2006 and fiscal year 2007 were carefully considered with respect to identifying the immediate needs and the urgent nature of the overall initiative. The most immediate needs are identified in the fiscal year 2006 supplemental request and the fiscal year 2007 request builds upon the activities identified in fiscal year 2006. In fiscal year 2006, total enacted funding for Pandemic activities is approximately \$24.8 million. Included in this number is the fiscal year 2006 \$20 million supplemental increase and approximately \$4.8 million in base spending. The \$20 million supplemental was received at the end of the first quarter of fiscal year 2006 and the funds were available on January 26, 2006.

The fiscal year 2007 total funding request for Pandemic Preparedness request is approximately \$55.3 million and includes the \$24.8 million from the fiscal year 2006 that includes the emergency supplemental appropriation and a requested increase of \$30.5 million over the fiscal year 2006 enacted level for pandemic influenza. We would be happy to provide the activities covered under the fiscal year 2006 supplemental request.

[The information follows:]

Food and Drug Administration Pandemic Influenza Request <i>(Dollars in Millions)</i>			
Pandemic Flu Vaccine Capacity	President's Proposed FY 2006 Supplemental	FTE	Description of Activities
CBER -- Enhance regulatory science base to facilitate new vaccines.....	16.7	75	Expand FDA capacity to facilitate the expedited development, evaluation and licensure of additional flu vaccines and manufacturing capabilities and capacity to meet pandemic preparedness needs, consistent with the DHH's Pandemic Influenza Strategic Plan. This includes developing and assessing new technologies, assuring the safety and effectiveness of vaccines, serving as consultants on product development and inspecting manufacturing facilities.
Office of Regulatory Affairs -- Post medical products/vaccines approval inspections.....	1.2	7	Experienced investigators will conduct bioresearch monitoring, drug manufacturer and flu vaccine manufacturer inspections, to assure product quality and prevent problems that threaten product safety or availability early in the development cycle. The requested resources will also allow ORA to expand current efforts to identify and intercept counterfeit products either claiming to prevent the flu or treat its symptoms.
Other Activities (OC) -- Office of Crisis Management/Office of Counterterrorism Policy.....	0.8	3	Support additional duties associated with strategic planning, policy leadership, coordination and communication of the FDA's pandemic influenza activities and design an agency-specific response to the threat of pandemic, consistent with the DHH's Pandemic Flu plan.
Other Activities (OM) -- IT/Systems Requirements.....	1.2	0	Modifications to IT Systems to ensure that critical information is available during the product life cycle.
Total FDA Request.....	20.0	85	

GENERIC DRUGS USER FEES/CITIZEN PETITIONS

Question. I understand that FDA believes it is time to implement a user fee program for generics. The generic drug industry has several criticisms of this idea. One is that they will still face many regulatory issues after their drug is approved. Another is that their budget has been chronically under funded—especially in relation to dollars spent approving new drugs, even without including user fee money.

How would you respond to these criticisms?

Answer. First, FDA has made significant investments to improve the generic drug review process with the funds appropriated by Congress. These investments have helped lower the median review time by 2 months. FDA has not made any decisions concerning a user fee program for generics. Given the existence of user fee programs for other product reviews, there have been suggestions that the idea may need to be explored, but these suggestions are general comments. There is no commitment to propose generic user fees and no formal Administration proposal for a generic user fee program. If a proposal is considered, we will certainly consider the concerns and criticisms about the proposal from the generic industry. We continue to work with the generic industry to address their current concerns with the Office of Generic Drugs.

Question. Have you begun working on legislation?

Answer. FDA has not made any decisions concerning a user fee program for generics, nor has the Agency begun work on legislation to enact such a program. Given the existence of user fee programs for other product reviews, there have been suggestions that the idea may need to be explored, but these suggestions are general comments. There is no commitment to propose generic user fees and no formal Administration proposal for a generic user fee program. If a proposal is considered, we will certainly consider the concerns and criticisms about the proposal from the generic industry. We continue to work with the generic industry to address their current concerns with the Office of Generic Drugs.

Question. It has been reported that one cause of unnecessary delays in getting generic drugs on the market are certain citizen petitions. I am aware that FDA is working on a study to figure out what the actual effects of these citizen petitions are. In last year's Senate report, we asked for an update on this study—including any changes FDA plans to make in the process. I understand that this report is still in your clearance process, but can you give us a preview of what we might be provided?

Answer. The Senate report is currently undergoing final clearance, but I would be happy to provide you with an overview of how FDA is addressing potential improvements to the citizen petition process. In response to the significant increase in the number of citizen petitions submitted to FDA's Center for Drug Evaluation and Research, CDER, and an increasing backlog of pending petitions, the Center's Office of Regulatory Programs or ORP, initiated an extensive review of CDER's processes for responding to citizen petitions.

The Office of Generic Drugs has made organizational changes designed to improve the citizen petition response process. The office has dedicated a specific group of scientists who will be responsible for addressing citizen petition responses. This organizational change is expected to increase the consistency, quality, and speed of the Office of Generic Drug's input on citizen petition responses.

ORP is currently undertaking an initial review of its citizen petition process improvement efforts. Although FDA has been implementing changes to its process for less than a year, the agency is trying to gather some early data to evaluate whether these new processes have been helpful and to examine whether additional improvements might be beneficial. The review and response to citizen petitions, however, requires careful and painstaking research, precise writing and editing, and thorough legal review to produce a document that is a clear representation of FDA's scientific and legal opinion of what are often very complex issues. This process requires input from many agency components.

In addition, ORP, the Office of Generic Drugs, and the Office of Chief Counsel plan to review blocking petitions that have been denied to consider such factors as the timing of the petition and the nature and age of the data upon which the petition was based. In some cases, individuals submitted petitions that were very close to the date of patent or exclusivity expiration were based on information that was readily available well before the petitions were submitted. Where we believe that further investigations may be warranted, the agency is considering the option to refer the cases to the Federal Trade Commission.

I would be happy to provide for the record a timeline for our recent activities related to improvements to the citizen petition process.

[The information follows:]

Timeline for Improvements to Citizen Petition Process

Fall of 2004.—ORP convened a process improvement team comprising representatives from ORP, the Office of New Drugs, and the Office of Generic Drugs and consulted with other offices involved in the petition process, such as the Office of Chief Counsel, to discuss improvements to the petition process.

October 2004 to May 2005.—The process improvement group generally met on a biweekly basis; sometimes more frequently. The group began by describing the existing process in detail and then looked for areas where FDA could make improvements and achieve efficiency.

June 2005.—ORP finalized new procedures to improve the citizen petition process and began full implementation of process improvements. ORP instituted some of these improvements while the meetings to identify improvements were ongoing.

May and June 2005.—ORP presented process improvement efforts to senior management within CDER and various groups involved in working on citizen petition responses.

Currently.—ORP is documenting its new procedures in a Manual of Policies and Procedures, also known as MAPP.

GENERIC DRUG APPROVAL

Question. I appreciate your response to my letter of February 6th, regarding generic drugs and the FDA strategic redeployment. However, there were some questions that were not answered.

What additional staffing and funding would be required to decrease the backlog of generic drug applications by 1/3 over the next fiscal year?

Answer. FDA understands that Congress and the public are concerned about the high cost of prescription drug products. Generic drugs play an important role in granting access to products that will benefit the health of consumers and the government. Prompt approval of generic drug product applications, also known as abbreviated new drug applications, or ANDAs, is imperative to making generic products available to American consumers at the earliest possible date. This has been a high priority for FDA.

FDA believes that making improvements in the process for the review of generic drug applications offers the best promise for reducing ANDA review time. 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, and has helped lower the median review time. In addition, FDA believes that making improvements in the process for the review of generic drug applications offers the best promise for reducing ANDA review time. With this goal in mind, in fiscal year 2005, FDA's Office of Generic Drugs, or OGD, focused on streamlining efforts to improve the efficiency of the ANDA review process. OGD added chemistry and bioequivalence review teams and has taken steps to decrease the likelihood that applications will face multiple review cycles. OGD also instituted revisions to the review process such as early review of the drug master file as innovator patent and exclusivity periods come to an end, cluster reviews of multiple applications, and the early review of drug dissolution data.

In fiscal year 2006, we will build on these process improvements. We have begun a major initiative to implement Question-based Review for assessment of chemistry, manufacturing, and controls data in ANDAs. This improvement builds on the Quality-by design and risk-based review initiatives of FDA's Center for Drug Evaluation and Research. This mechanism of assessment is consistent with the International Conference on Harmonization Common Technical Document and will enhance the quality of evaluation, accelerate the approval of generic drug applications, and reduce the need for supplemental applications for manufacturing changes.

FDA's OGD will continue institute efficiencies in the review process to accelerate the review and approval of ANDAs. FDA will also continue to work very closely with the generic manufacturers and the generic drug trade association to educate the industry on how to submit applications that can be reviewed more efficiently and that take advantage of electronic efficiencies that speed application review. We will also work with new foreign firms entering the generic drug industry. The agency recognizes that it will take time for these new firms to understand the requirements for generic drug products. In the long term, however, these efforts should shorten overall approval time and increase the number of ANDAs approved during the first cycle of review. In fiscal year 2006, FDA plans to spend \$62.8 million relating to generic drugs and, specifically, \$28.3 million in OGD. In fiscal year 2007, FDA plans to spend \$64.6 million relating to generic drugs and \$29 million in OGD.

Question. What additional staffing and funding is required to decrease the length of time it takes to approve a generic drug application by 25 percent?

Answer. FDA recognizes that generic drugs play an important role in granting access to products that will benefit the health of consumers and the government. The total spending on the Generic Drugs Program is \$64.6 million, which is more than a 66 percent increase from the comparable fiscal year 2001 amount. This has helped lower median drug review time by 2 months. FDA believes that making improvements in the process for the review of generic drug applications offers the best promise for reducing Abbreviated New Drug Application, also known as ANDA, review time. With this goal in mind, in fiscal year 2005, FDA's Office of Generic Drugs, or OGD, focused on streamlining efforts to improve the efficiency of the ANDA review process. In fiscal year 2006, we will build on these process improvements, including efforts to implement Question-based Review. FDA's OGD will continue institute efficiencies in the review process to accelerate the review and approval of ANDAs. FDA will also continue to work to educate the industry on how to submit applications that can be reviewed more efficiently. We will also work with new foreign firms entering the generic drug industry. The agency recognizes that it will take time for these new firms to understand the requirements for generic drug products. In the long term, however, these efforts should shorten overall approval time and increase the number of ANDAs approved during the first cycle of review.

Question. Please provide the number of new drug applications that have been submitted and approved in each of the last 5 years, including the average timeframe for approval. How does this number compare with the number of generic drugs that have been submitted and approved?

Answer. I would be happy to provide that information for the record.
[The information follows:]

The following two tables provide a 5-year summary of approval statistics for new drugs. Please note: The submissions approved in a particular fiscal year are not necessarily filed in that fiscal year.

APPROVAL TIMES FOR PRIORITY AND STANDARD NEW DRUG AND BIOLOGIC APPROVALS, NDAS/BLAS FISCAL YEARS 2001 TO 2005—APPROVAL TIMES IN MONTHS

Fiscal year	Priority			Standard			
	Submissions Filed	Number Approved	Mean Approval Time	Submissions Filed	Number Approved	Mean Approval Time	Median Approval Time
2001	10	10	7.9	86	61	17.8	15.0
2002	12	10	14.3	84	54	19.4	14.8
2003	19	14	18.2	82	72	21.9	13.3
2004 ¹	28	19	13.8	94	74	19.7	12.7
2005 ¹	32	27	10.1	71	82	20.6	12.9

¹Beginning in fiscal year 2004, CDER figures include BLAs for therapeutic biologic products which were transferred from CDER to CBER.

APPROVAL TIMES FOR PRIORITY AND STANDARD NEW MOLECULAR ENTITIES, NMEs AND NEW BIOLOGICS FISCAL YEARS 2001 TO 2005—APPROVAL TIMES IN MONTHS

Fiscal Year	Priority NMEs/New Biologics ¹			Standard NMEs/New Biologics ¹			
	Number Filed	Number Approved	Mean Approval Time	Number Filed	Number Approved	Mean Approval Time	Median Approval Time
2001	8	5	8.5	24	10	24.7	21.9
2002	8	8	13.7	14	14	16.4	12.5
2003	12	8	9.0	17	13	21.6	22.8
¹ 2004	18	13	12.7	15	14	22.8	19.3
¹ 2005	18	17	12.4	14	10	25.5	23.9

¹Beginning in fiscal year 2004, CDER figures include BLAs for therapeutic biologic products which were transferred from CDER to CBER.

The following table provides information regarding generic drug approvals

APPROVAL TIMES FOR GENERIC DRUG FISCAL YEARS 2001 TO 2005—APPROVAL TIMES IN MONTHS

Fiscal Year	Receipts of Original ANDAs	Number of Approvals	Mean Approval Time	Median Approval Time
2001	307	241	20.9	18.4
2002	361	296	21.4	18.3
2003	449	284	20.7	17.3
2004	563	320	20.5	16.3
2005	766	361	19.5	16.3

Question. What total funding has been spent annually on approval of new drugs for the past 5 years? Please list appropriated funding and user fees separately.

Answer. I would be happy to provide the amount spent annually on the approval of new drugs in the past 5 years for the record.

[The information follows:]

FUNDING TOTALS FOR NEW DRUGS

	Amount
Fiscal year 2001:	
Appropriated Funding	\$76,000,000
User Fees	47,500,000
Total	123,500,000
Fiscal year 2002:	
Appropriated Funding	70,000,000
User Fees	49,300,000
Total	119,300,000
Fiscal year 2003:	
Appropriated Funding	75,000,000
User Fees	56,500,000
Total	131,500,000
Fiscal year 2004:	
Appropriated Funding	72,000,000
User Fees	76,900,000
Total	148,900,000
Fiscal year 2005:	
Appropriated Funding	75,200,000
User Fees	83,400,000
Total	158,600,000

DRUG ADVERTISING

Question. I understand that FDA issued approximately 15 warning letters to drug companies regarding advertisements in 2005, an increase from the past several years. As we all know, though, the number of drugs ads has also increased. I am pleased that drug companies have published guidelines for their ads, and appear to be working with the FDA to try to ensure that ads are more responsible and presented fairly. I believe FDA is working on guidance to be published this year to assist drug companies in that effort.

Can you give us an update on FDA's activities relating to drug ads? Is it still FDA's position that companies should not be required to submit ads to FDA prior to their publication?

Answer. On November 1 and 2, 2005, the FDA held a two-day public hearing to provide an opportunity for broad public participation and comment on direct-to-con-

sumer, also known as DTC, promotion of regulated medical products, including prescription drugs for humans and animals, vaccines, blood products, and medical devices. FDA is in the process of developing additional guidance for industry. Our major effort is a draft guidance to address the presentation of risk information in prescription drug and medical device promotion. Another effort is to finalize the draft guidance on the brief summary of risk information for the page adjacent to direct-to-consumer print advertisements for prescription drugs. FDA will conduct a series of three studies to examine the format and content of brief summaries in direct-to-consumer print advertisements to assist the agency in finalizing this draft guidance. FDA is also working to finalize the draft guidance on criteria FDA uses to distinguish between disease awareness communications and promotional materials, to encourage manufacturers to disseminate educational messages to the public, and the guidance on the manner in which restricted device firms can comply with the rules for disclosure of risk information in consumer-directed broadcast advertising for their products. FDA has created a Promotion Steering Committee to leverage policy development for prescription drug promotion, including DTC promotion. The committee consists of representatives from the Office of the Commissioner, Office of Chief Counsel, and each center responsible for medical products. The committee meets to determine how to best allocate our limited resources for policy development.

Under current law and regulations, FDA cannot require companies to submit promotional materials prior to use. In addition, there are tens of thousands of promotional pieces per year, prior review, even if authorized, would be a major challenge.

Question. If legislation were enacted calling for prior approval of prescription drug ads before airing, would your agency have adequate personnel and resources to meet this mandate? Could you provide us more information on this?

Answer. The Administration has not established a position on the legislative proposal you describe. The Center for Drug Evaluation and Research receives over 54,000 pieces per year, of which 9,000 are direct-to-consumer, or DTC. Of the 9,000 pieces of DTC final materials, only 467 are sent in as proposals. Providing timely review of these promotional material would represent a tremendous increase in workload and FDA could not conduct timely reviews of these promotional material with the resources available.

FDA feels that it is highly valuable to the public for us to review and provide advice to manufacturers about broadcast advertisements while they are being produced. Therefore, we have made that one of our highest priorities. This helps ensure DTC compliance and reduces the number of advertisements that might otherwise violate the Food, Drug & Cosmetic Act from appearing in public.

FOOD DEFENSE

Question. Dr. Von Eschenbach, the past several years have seen huge increases for "food defense": \$20.5 million in fiscal year 2004, \$35.5 million in fiscal year 2005, \$10 million in fiscal year 2006, and the budget this year proposes an increase of nearly \$20 million.

In your written statement, you spend just under two pages discussing what this money will buy. FERN Labs, eLexnet systems, and Emergency Operations Networks all sound, and I'm sure in fact are, very important, but this is a lot of money, and I think we should spend a little more time focusing on it—especially if these increases are coming at the expense of other activities.

Can you walk us through a scenario that illustrates how this money will be used, in a practical way, to prevent or contain an outbreak involving contaminated food of drugs? How are we safer now that all of this money has been spent?

Answer. In one such scenario, a truck driver for a food manufacturing plant introduces a biological, chemical, or radiological agent into truck loads of a byproduct en route between the food manufacturing plant and one of several plants that converts the byproduct into a usable food ingredient. The food ingredient is distributed nationwide as well as overseas. The ingredient is used in the manufacture of a variety of seemingly unrelated food items. Many of these food items are themselves used as ingredients in other foods. Consequently, contaminated ingredients from several plants would end up in a large number of foods, under a variety of brand names, with national distribution.

Food Emergency Response Network, or FERN, laboratory testing in the scenario listed above would likely include finished product testing of foods implicated in human illness; and, food of the same lots as those implicated in human illness at various points in the production and distribution systems totaling approximately 100,000 samples for analysis. To fully recover from this scenario or from a terrorist

attack or national emergency, FDA would need to conduct recalls, seizures, and/or disposal of contaminated food which would then restore confidence in the Nations food supply.

Food Defense funding supports FDA's five key areas of awareness, prevention, preparedness, response, and recovery. FDA strives to increase awareness of the role of food as a vehicle for terrorism, various illnesses, and symptoms that are caused by foodborne threat agents; and, by educating and coordinating the dissemination of information to State and local partners, relevant associations, and industry. With Food Defense funding, FDA is able to conduct surveillance, inspectional and sampling programs to monitor manufacturers and their products for the presence of threat agents where such an intentional tampering may be found prior to full human consumption. FDA studies food prevention technologies to improve the safety of food and establish guidelines and or performance standards for industry which might prevent the contamination altogether. FDA has worked on method validation and matrix extension to strengthen the Nation's food testing laboratory capability in order to be prepared to quickly detect threat agents in the food supply. In addition, the FERN provide response capabilities by rapidly testing large numbers of samples of food. The Emergency Operations Network, or EON, is an enhanced communication system that provides seamless information access to all FDA offices, enabling them to respond quickly to the full range of FDA emergencies.

Question. With regard to the technology we are buying and labs we are outfitting—are they flexible? Can they be used for other activities when there are no emergencies? How do they complement or duplicate similar USDA labs?

Answer. Many of the agents we are concerned about in food defense are also of food safety concern. Therefore, the equipment is useful for our routine food safety surveillance programs as well as food defense activities. The state Food Emergency Response Network, or FERN, Chemistry laboratories that were awarded FDA FERN chemistry Cooperative Agreements in fiscal year 2005 are utilizing the equipment and resources provided by FDA to increase capability of FERN analytical methods and for surveillance of the food supply. Currently, these laboratories are actively engaged in increasing the number of analytes and food commodities that the current FERN Chemistry methods can detect. This method validation work not only increases the capabilities of the Cooperative Agreement laboratories but also increases the capabilities of the entire FERN Network when the expanded methods are shared with all FERN Chemistry laboratories.

In addition, the Cooperative Agreement laboratories are involved in the surveillance of the food supply through ad hoc analysis of food commodities for Food Defense analytes. These surveillance analyses are based on vulnerability and risk assessments. This surveillance sampling provides a wider food shield and an opportunity to demonstrate and assess the capabilities, capacity, and communication within the FERN. Cooperative Agreement laboratories also analyze proficiency test samples throughout the year to demonstrate their continuing capability to analyze particular food commodities for identified analytes. These proficiency test samples build confidence in each laboratory's ability to find threat agents in a variety of food commodities, were there to be terrorist attack or a national emergency.

To avoid duplication, FDA has taken the lead in funding both Chemistry and Radiological FERN laboratories to build capability and capacity for these disciplines across the Nation, whereas United States Department of Agriculture, or USDA, is responsible for funding the Microbiological laboratories. Therefore, our coordinated efforts are complementary to FDA's overall FERN program.

Question. Do you anticipate a time we won't have to provide huge increases every year for these activities—when will we simply be able to maintain our safeguards?

Answer. Thank you for the opportunity to address FDA's efforts to safeguard the food supply from attack. FDA regulates \$240 billion worth of domestic food and \$15 billion of imported food. The American food industry contributes approximately 20 percent of the U.S. Gross National Product, employs about 14 million individuals, and provides an additional 4 million jobs in related industries. FDA's capacity to defend the food supply from attack and to maintain consumer confidence in our ability to do so has significant impacts on the public health and the Nation's economy.

Our plan for food defense aligns with the mandate of Homeland Security Presidential Directive-9, which establishes a national policy to defend the food and agriculture system. Among the key food defense projects funded to date is the Food Emergency Response Network, or FERN. FERN establishes and expands a national laboratory network to increase analytic surge capacity for biological, chemical and radiological agents in food. Other key food defense projects include targeted food defense research; targeted, risk-based inspections; Biosurveillance, to improve coordination and integration of existing food surveillance capabilities under the government-wide Biosurveillance Initiative; and emergency Operations Network Incident

Management System, to upgrade and expand FDA's management and coordination capabilities for responding to incidents affecting the U.S. food supply.

FDA conducts these activities in the context of an ever-increasing volume of imported foods and the growing complexity of the food industry and of the technologies used in food production and packaging. This transformation will continue to present fresh challenges for FDA and for the plans and strategies we use to defend the food supply from attack. We will direct any food defense funding provided in fiscal year 2007 to address these new challenges, to build upon past successes, and to strengthen our capabilities to address terrorist threats to the food supply.

Although the Administration has not formulated a budget for fiscal year 2008 and later years, the long-term recommendation for the FERN program is for FDA to achieve a total of 50 state laboratories. With the funding in our fiscal year 2007 budget, we estimate that we will increase the number of operational facilities to 16 laboratories. You are correct in pointing out that we will not need budget increases to expand the number of FERN laboratories once we establish all of these labs. However, there may still be an annual need for resources to maintain and support FERN labs.

UNIFORM FOOD SAFETY

Question. Does FDA support the National Uniformity for Food Act as passed recently in the House of Representatives? Please explain why or why not.

Answer. The Administration has not taken a position on this legislation.

POST-MARKETING STUDIES

Question. What activities, if any, is FDA undertaking in order to decrease the number of post-marketing studies that have been pledged to FDA but not yet undertaken? Does FDA see this as a problem? Why or why not?

Answer. Postmarketing Study Commitments, also known as PMCs, for approved drug products, including biological drugs, are studies that a product sponsor either is required or agrees to conduct after FDA approves a product for marketing to further define the safety, efficacy, or optimal use of a product. FDA closely monitors the status of PMCs to ensure that product sponsors initiate and complete the studies in a timely manner. In some cases, the studies can take years to complete, even if everything is on schedule. In other cases, there are considerable obstacles, such as difficulty in recruiting patients and investigators to participate in a clinical trial when an approved therapy is available. Sponsors must resolve these issues before they can complete the studies. When obstacles arise, FDA works closely with sponsors to address these obstacles. 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. Depending on the complexity of the study, FDA would expect that many of these studies would not have been initiated yet.

As of the Senate Hearing date, FDA had planned to undertake a review of the decision-making process behind requests for PMCs but had not formally issued a contract. On April 5, 2006, FDA awarded a contract to an outside organization to conduct a thorough evaluation of the postmarketing study commitment process for collecting medical information. The contractor will examine in-depth the agency's internal processes regarding PMCs and make recommendations regarding ways to improve FDA's PMC processes and practices. The outside contractor will evaluate how review divisions decide whether to request PMCs, how divisions make decisions surrounding what kinds of PMCs to request, and how divisions establish reasonable timeframes for completing PMCs. The study will serve to assist FDA in determining whether industry needs better guidance regarding PMCs and to ensure there is a standardization of the procedures. In addition, the Centers within FDA also have undertaken activities to improve the response on postmarketing and post-approval studies.

FDA takes its statutory obligations under the Food and Drug Administration Modernization Act of 1997 to track and monitor the progress of PMCs very seriously. FDA recently published a final guidance for 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 basic information that FDA committed 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.

On January 1, 2005, the Center for Devices and Radiological Health, also known as CDRH, initiated the use of the new Condition of Approval Tracking System. As

of that date, all postapproval studies are entered into the system, along with the due dates of any agreed upon report deliverables. CDRH monitors the system 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. Under the new system, all reports have been delivered on time.

CDRH is also developing the Postapproval Study Web site that will be available to the public. This Web site will list the postapproval 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 follow-up on overdue reports will encourage compliance. Finally, we believe the public Web site will prompt industry to conduct the studies and report to FDA on time.

MICROBIOLOGICAL DATA PROGRAM

Question. The USDA is proposing to eliminate that Microbiological Data Program, currently carried out by the Agricultural Marketing Service. One reason offered for this proposal is that FDA currently undertakes, or will continue, the work of this program. Reports of increased food illnesses from fruits and vegetables appear to highlight the importance of the Microbiological Data Program.

Has FDA worked with AMS in order to ensure that none of the sampling currently carried out through the Microbiological Data Program will be eliminated?

Answer. As a science-based agency, FDA collects data that can be used to direct policy decisions, risk assessments, regulatory actions, and other actions. In comparison, the Microbiological Data Program, or MDP, program of the USDA Agricultural Marketing Service, also called AMS, is a non-regulatory sampling survey. Because the MDP program is not bound by the same regulatory requirements as FDA, it provides an opportunity for collection of a much larger data set. However, the MDP is not designed to provide the same source information, traceback, or support for regulatory follow-up that are built into the FDA sampling assignments. If a positive sample is found in an FDA produce sampling assignment, follow-up action can be taken, while the design of the MDP program does not allow for follow-up. Therefore, if AMS does eliminate the MDP program, it would not produce a surveillance gap as FDA defines this term.

Question. Is FDA already working on similar activities?

Answer. Since 1999, FDA has routinely issued sampling assignments for selected commodities produced both domestically and abroad. The purpose of FDA's produce sampling assignments is to gather information on both the incidence of contamination and the practices and conditions associated with contaminated produce and to take regulatory action, as appropriate, when contaminated produce is found. The FDA sampling assignments differ from the Agricultural Marketing Service's Microbiological Data Program, also known as MDP, in important ways. FDA samples are routinely collected at the farm gate or packinghouse for domestic produce or at the border for imported produce. With domestic samples, if contamination is present, it must have occurred at the farm or packing facility. MDP samples are routinely collected at a later stage of the supply chain, such as a distribution center, making it more difficult to narrow down where contamination might have occurred. The MDP program is a blind study. It does not collect information about the samples that would allow traceback to the source; therefore, it does not provide an opportunity to visit farms or packinghouses associated with positive sample to gather information about practices or conditions at those firms that may have led to contamination. FDA samples are tested in FDA laboratories, while MDP samples are tested at state laboratories. FDA data have a relatively well known performance standard across the United States.

QUESTIONS SUBMITTED BY SENATOR TOM HARKIN

AFLATOXIN

Question. Late last year, a pet food company based in South Carolina initiated a recall of dog food that had been made with corn contaminated with aflatoxin, produced by mold that sometimes develops in crops under drought or other weather stress conditions. The death of dozens of dogs has been attributed to consumption of this product both before and after the recall was announced.

What steps has FDA taken to address this situation to ensure the recall is fully and effectively completed?

Answer. FDA determined that this situation represented a serious life-threatening health hazard to pet dogs and pet cats and classified this recall as Class I. In a Class I Recall, FDA requests that the firm conduct 100 percent effectiveness checks of their consignees to confirm that they received notification about the recall and have taken appropriate action. Additionally, our Atlanta district office issued audit check assignments in coordination with the Center for Veterinary Medicine to determine the effectiveness of the company's recall. The vast majority of FDA audit checks are completed and show the recall of dog food to be effective. FDA will monitor the disposal of all recovered products. FDA will terminate this recall when disposition of the recalled products is finalized.

Question. How can we assure the pet owners of this country that this kind of event won't happen again?

Answer. As part of the investigation, FDA evaluated the company's descriptions of the actions it has implemented at all of its plants to ensure that an aflatoxin event does not happen again and found the corrective actions acceptable. This situation generated much attention and has served as a reminder to the pet food industry of the importance of using appropriate manufacturing and quality control procedures.

BIOTERRORISM

Question. In December of 2004, the outgoing Secretary of Health and Human Services Tommy Thompson stated "I, for the life of me, cannot understand why the terrorists have not attacked our food supply, because it is so easy to do." The President's 2007 budget increases funding for food defense to continue lab preparedness efforts and expand State laboratories. However, it cuts funding for food import inspections at ports of entry which a terrorist might use to smuggle contaminated food products into the country. Since 1994, food imports have grown five-fold to 6 million food import shipments annually, but the FDA inspects less than 2 percent of these shipments.

Won't these proposed budget cuts for import inspection and testing actually weaken FDA's ability to prevent an attack on the food supply and make more likely the event that Secretary Thompson predicted?

Answer. For fiscal year 2007, FDA is requesting an increase of \$19.9 million in food defense to a total request of \$178.2 million. This is a 21,500 percent increase in funds from fiscal year 2001. The funds requested would continue to improve laboratory preparedness and food defense field operation, food defense research, surveillance, and incident management capabilities. FDA uses a risk-based approach to allocate resources. By focusing on risk through the cooperative work of Customs and Border Protection, or CBP, FDA's Prior Notice Center, and FDA field examinations, we will work smarter to target higher risk products, manufacturers, and importers to ensure the safety of the public health, protect the Nation's food supply and prevent an attack on the Nation's food supply.

For example, currently, working with information submitted through CBP's electronic systems used for import entries or through FDA's internet-based Prior Notice System Interface, FDA screens shipments electronically before they arrive in the United States to determine if the shipments meets identified criteria for physical examination or sampling and analysis or warrants other review by FDA personnel. This electronic screening allows FDA to better determine how to deploy our limited physical inspection resources at the border on what appear to be higher-risk food shipments while allowing lower-risk shipments to be processed in accordance with traditional import procedures after the electronic screening.

Question. Instead of cutting border inspection, shouldn't the Bush administration apply more resources to food import inspections to bolster our defenses against bioterrorism?

Answer. Through smart allocation of FDA resources, fine tuning FDA's risk based approach, and smarter screening criteria, the FDA will be able to continue ensuring a safe food supply and protecting the public health despite cuts in border inspections, which will allow funding to other higher risk food defense and lab preparedness areas.

SUNSCREEN

Question. Skin cancer is on the rise in the United States. A significant contributor is exposure to UVA rays. FDA has been developing a monograph for sunscreens since 1978 to address the critical issue of UVA rays but has not, thus far, issued it. As part of the Fiscal year 2006 Agriculture Appropriations Act, FDA was asked

to issue a “comprehensive final monograph for over-the-counter sunscreen products, including UVA and UVB labeling requirements within 6 months of enactment.”

What is the status of the monograph?

Answer. We are currently working on a rulemaking for OTC sunscreen drug products to address both UVA and UVB labeling requirements.

Question. Will the monograph be issued by May 10th, the date the fiscal year 2006 Act requires?

Answer. We are working to publish the document for this rulemaking in the Federal Register.

GENERIC DRUGS

Question. Generic drugs help to make health care more affordable. Currently, FDA has a backlog of 850 applications for generic drugs—there are expected to be more over the next several years. Yet, the President’s budget flat funds the Office of Generic Drugs. In your testimony before the Committee, you stated that generics were reviewed in priority order, meaning that new generics for branded drugs without a generic counterpart would be bumped to the front of the line. However, more price competition between generics is also a valuable way to decrease the price consumers pay for drugs. Therefore, I believe prioritization is not, in and of itself, a sufficient solution to the problem. In addition, approval delays effectively extend the patent life of branded drugs despite Congress’ clear intention otherwise. FDA has increased its generic drugs Full Time Evaluators (FTEs) from 134 in 2001 to 201 in 2006. Despite the increase, I am concerned FDA is not devoting enough personal and resources to generic drugs given the current workload and the future increase.

How many FTEs would be required to eliminate the current backlog within the next year?

Answer. FDA understands that Congress and the public are concerned about the high cost of prescription drug products. Generic drugs play an important role in granting access to products that will benefit the health of consumers and the government. Prompt approval of generic drug product applications, also known as abbreviated new drug applications, or ANDAs, is imperative to making generic products available to American consumers at the earliest possible date. This is a key priority for FDA. Since 2001, FDA has increased spending on the Generic Drugs Program to \$64.6 million for fiscal year 2007, which is more than a 66 percent increase from the comparable fiscal year 2001 amount. This has allowed FDA to reduce median review time by 2 months.

FDA believes that making improvements in the process for the review of generic drug applications offers the best promise for reducing ANDA review time. With this goal in mind, in fiscal year 2005, FDA’s Office of Generic Drugs, or OGD, focused on streamlining efforts to improve the efficiency of the ANDA review process. OGD added chemistry and bioequivalence review teams and has taken steps to decrease the likelihood that applications will face multiple review cycles. OGD also instituted revisions to the review process such as early review of the drug master file as innovator patent and exclusivity periods come to an end, cluster reviews of multiple applications, and the early review of drug dissolution data.

In fiscal year 2006, we will build on these process improvements. We have begun a major initiative to implement Question-based Review for assessment of chemistry, manufacturing, and controls data in ANDAs. This improvement builds on the Quality-by design and risk-based review initiatives of FDA’s Center for Drug Evaluation and Research. This mechanism of assessment is consistent with the International Conference on Harmonization Common Technical Document and will enhance the quality of evaluation, accelerate the approval of generic drug applications, and reduce the need for supplemental applications for manufacturing changes. FDA believes that these process improvements will work to make more generic drugs available to the public.

FDA’s OGD will continue institute efficiencies in the review process to accelerate the review and approval of ANDAs. FDA will also continue to work very closely with the generic manufacturers and the generic drug trade association to educate the industry on how to submit applications that can be reviewed more efficiently and that take advantage of electronic efficiencies that speed application review. We will also work with new foreign firms entering the generic drug industry. The agency recognizes that it will take time for these new firms to understand the requirements for generic drug products. In the long term, however, these efforts should shorten overall approval time and increase the number of ANDAs approved during the first cycle of review. In fiscal year 2006, FDA plans to spend \$62.8 million relating to generic drugs and, specifically, \$28.3 million in OGD. In fiscal year 2007, FDA plans to spend \$64.6 million relating to generic drugs and \$29 million in OGD.

Question. How much would that cost?

Answer. FDA recognizes that generic drugs play an important role in granting access to products that will benefit the health of consumers and the government. FDA believes that making improvements in the process for the review of generic drug applications offers the best promise for reducing ANDA review time. With this goal in mind, in fiscal year 2005, FDA's Office of Generic Drugs, or OGD, focused on streamlining efforts to improve the efficiency of the ANDA review process. In fiscal year 2006, we will build on these process improvements, including efforts to implement Question-based Review. FDA's OGD will continue institute efficiencies in the review process to accelerate the review and approval of ANDAs. FDA will also continue to work to educate the industry on how to submit applications that can be reviewed more efficiently. We will also work with new foreign firms entering the generic drug industry. The agency recognizes that it will take time for these new firms to understand the requirements for generic drug products. In the long term, however, these efforts should shorten overall approval time and increase the number of ANDAs approved during the first cycle of review.

Question. Does FDA estimate the number of future Abbreviated New Drug Applications when making decisions to allocate resources to hiring and training FTEs?

Answer. FDA attempts to project application numbers by ongoing tracking of receipts and by looking at the products that will be going off patent as well as other industry forecasts of trends. FDA also ensures that it can meet the specified budget earmark for the generic drug review program.

EARLY FOOD SAFETY EVALUATION

Question. I understand your agency is nearing publication of its final Early Food Safety Evaluation, (EFSE) guidelines. I'm happy to hear that as it is an important issue for American agriculture and I look forward to its release.

Can you offer us more specifics on when we can expect to see final publication?

Answer. We are moving to complete the last steps necessary to finalize the guidance. For example, we are currently nearing completion of the requirements of the Paperwork Reduction Act of 1995. The comment period for the Notice for the agency information collection activities recently closed on March 13, 2006. We expect publication soon after completion of these final steps.

FOOD IMPORTS

Question. More than 80 percent of the seafood and an estimated 20 percent of fresh produce that Americans consume is imported. 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, killing at least 3. There are many other examples of contaminated food that caused large scale outbreaks and fatalities in the last 10 years.

How do you intend to improve FDA's oversight of imported food?

Answer. FDA will continue to implement the Public Health Security and Biodefense Preparedness and Response Act of 2002, which provides FDA with authorities aimed at enhancing the security of imported foods. For example, the requirement for domestic and foreign facilities to register with FDA will help FDA quickly identify, locate, and notify the facilities that may be affected in the event of a potential or actual terrorist incident or outbreak of foodborne illness. The advance information about imported food shipments, provided under the prior notice requirement, enables FDA, working closely with Customs and Border Protection, or CBP, to more effectively target inspections of food at the border at the time of arrival to ensure the safety and security of imported food. This advance notice not only allows FDA's and CBP's electronic screening systems to review and screen the shipments for potential serious threats to health, intentional or otherwise, before food arrives in the United States, but it also allows FDA staff to review prior notice submissions for those products flagged by the systems as presenting the most significant risk and determine whether the shipment should be held for further investigation.

For fiscal year 2007, FDA is requesting an increase of \$19.9 million in food defense to a total of \$178.2 million. This is a 21,500 percent increase in funds from fiscal year 2001. The funds requested would continue to improve laboratory preparedness and food defense field operation, food defense research, surveillance, and incident management capabilities.

FDA has worked to develop an automated risk-based import entry examination system. This system is designed to assess risk in individual import shipments. The system will combine expert knowledge, open source intelligence and advanced self-learning algorithms to dynamically assess entry-line level risk. In 2005, the first of a series of research and analysis papers on this system provided timely and relevant

information to serve as the basis for exogenous-source rules development for risk-based import examination. The goal in the project is to provide early identification and assessment of events, conditions, and situations in the world that could have an impact on the safety or security of FDA-regulated imports. The project is currently focused on imported seafood.

Question. How much would it cost to increase food import inspections from 2 percent to 5 percent or 10 percent?

Answer. During fiscal year 2005, the Field conducted approximately 85,000 Import Food Field Exams/Tests; analyzed approximately 25,550 food import lab samples; and, made 8,672,168 Import Line Decisions. Over 1.27 percent of food import lines were physically examined during fiscal year 2005. In addition, critical steps in our counter terrorism efforts are the Prior Notice Security Import Reviews. During fiscal year 2005, the Field conducted 86,187 Prior Notice Security Import Reviews in the foods area.

The mission of FDA's Prior Notice Center, or PNC, is to identify imported food and feed products that may be intentionally contaminated with biological, chemical or radiological agents, or which may pose significant health risks to the American public, and intercept them before they enter the United States. FDA will continue to focus resources on Prior Notice Import Security Reviews of products that pose the highest potential bioterrorism risks. The PNC uses a combination of adaptable targeting strategies and weighted risk indicators in the threat assessment process including contemporary intelligence involving terrorist activities, a history of prior notice violations, and compliance with admissibility standards as indicated by the results of import field exams, filer evaluations, firm inspections, repeated prior notice violations, and feedback from Field Investigators. By using a risk based approach, the Prior Notice Center can intercept potentially hazardous products before they enter the United States.

The benefit of these reviews comes from the quality and targeting of review activities; not from the volume of imports inspected. Thus, the quality of import screening is a better measure of FDA's import strategy rather than simply focusing on the items physically examined.

Question. Could FDA improve its oversight of imports if it had inspectors checking farms and factories in the country where our food originates?

Answer. FDA continues to enhance our risk based approach to target higher risk products, manufacturers, and importers with available resources. FDA-conducted foreign inspections are an important aspect of this multifold approach. It is important to understand, however, that this is only one component of our approach. We also use previous examination and laboratory sampling results, compliance information received from other domestic and foreign regulatory agencies, examination at the ports of entry, and general risk factors posed by the products in question to provide controls of the safety of import food commodities. FDA also focuses on risk by working cooperatively with Customs and Border Protection and through the FDA's 24/7 Prior Notice Center in counter- and bioterrorism targeting and evaluation of supply chain integrity.

Although foreign inspections and border operations provide some assurance that imported foods are safe, the agency continues to work to foster international agreements and harmonize regulatory systems. For example, we actively participate in the Canada/United States/Mexico Compliance Information Group, which shares information on regulatory systems and the regulatory compliance status of international firms to protect and promote human health. In addition, FDA is heavily involved in the Codex Alimentarius Commission Committees, which develop Codes of Practice and standards to harmonize international food safety practices.

FOOD RECALL

Question. The Food and Drug Administration (FDA) does not have mandatory authority to recall contaminated food products and instead relies on voluntary cooperation by food companies to get contaminated food out of supermarkets, restaurants, and consumers' homes. In a recent GAO study, FDA identified over 3,000 recalls of non-meat and poultry foods from 1986 to 1999 and GAO identified nine instances during that time where companies delayed or refused compliance with an FDA recall request.

Should FDA have mandatory recall authority in order to protect American consumers from contaminated food? Why or Why not?

Answer. The vast majority of food recalls are initiated voluntarily by firms when a problem is discovered, often after the product has entered the marketplace. It is the responsibility of the recalling firm to account for product remaining under its direct control, to quickly notify direct consignees of the identity of the product and

any potential hazard that it presents, and to request subrecalls where indicated. FDA monitors recalls and either discusses follow-up actions with the firm if it appears that the recall is not effective, or if necessary, takes direct action to complement actions taken by the firm. FDA encourages firms to conduct recalls that are effective and may take enforcement action to remove products from the market if a firm is unable or unwilling to do so.

When the hazard is significant, FDA expects that firms will initiate a public notification process to make the public aware of the problem and to recommend steps to be taken in order to prevent injury or illness. Recall notifications provide the corrective action necessary and a means for returning and/or reporting the status of the recalled product.

In the event that public notice is not provided or is not sufficient, FDA has and will continue to notify the public of the hazard.

Question. If a terrorist attack against the food supply occurred, how would FDA ensure the food was removed from the distribution chain, supermarket shelves, and people's homes?

Answer. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 includes a number of provisions that give new authority to FDA to take action to protect the food supply against the threat of intentional or accidental contamination of the food supply. If a terrorist attack on the food supply occurs, FDA would work with State and local food safety officials to remove products from store shelves and distribution channels. FDA would also work with the press to alert the trade industry and consumers about the potential hazard and would provide consumers with information on how and where to dispose of contaminated foods. We would include information to consumers on what they should do if they had been exposed to the contaminated food.

To ensure efficiency if an emergency occurred, FDA continues to take additional measures to improve the success of recalls. On November 3, 2003, FDA posted guidance to the industry on our website intended to assist industry in handling all aspects of a product recall, including all corrections and removals. We also continue to develop the Recall Enterprise System, which, when completed, will post recalls on our website in real time.

METHYLMERCURY

Question. FDA and EPA have issued a joint advisory warning pregnant women and women planning a pregnancy to avoid swordfish, shark, some types of tuna and king mackerel, since those fish accumulate large quantities of methylmercury which can harm their unborn children. Eating seafood is the leading cause of exposure to methylmercury, a toxin that can cause neurological damage to the developing fetus and young children.

Although the advisory is useful, some groups have complained that it is complicated and hard-to-remember. The Center for Science in the Public Interest recently recommended that all grocery stores and fish retailers should post the warning at the counter where consumers actually purchase the seafood.

Why doesn't FDA enforce the limit for methylmercury in seafood, e.g. test and remove seafood from the market that exceeds the limit of 1 ppm?

Answer. Risk from methylmercury is generally understood to derive from substantial exposure over time of many meals that include fish. That is why we issued a consumer advisory on methylmercury directed toward women of childbearing age and young children. We are conducting surveys to determine how the public, including pregnant women and health care providers, are reacting to the consumer advisory on methylmercury and to other information they may be receiving from all sources about seafood risks and benefits.

It is useful to note that data from the National Health and Nutrition Examination Survey, operated by the Centers for Disease Control and Prevention, that measures levels of methylmercury in U.S. women of childbearing age and young children through 5 years of age reveal that the overwhelming majority of both women of childbearing age and young children are exposed to methylmercury at very low levels. The next phase of our risk management process for methylmercury involves a risk analysis that is examining the likelihood of adverse effects through the range of exposures being experienced by U.S. consumers. This project is also examining the likelihood of health and nutritional benefits from eating fish at various levels of consumption.

Question. To make the advisory truly effective, why doesn't FDA require point-of-purchase notices giving consumers detailed information on which types of fish contain high levels of methylmercury at the fish counter?

Answer. FDA, in conjunction with the Environmental Protection Agency, or EPA, has implemented a cost-effective public education campaign. This campaign is designed to inform high-risk consumers about reducing their exposure to high levels of mercury, while emphasizing the health benefits of consuming fish and shellfish. This has resulted in raising awareness about methylmercury in seafood. We believe the steps that have been taken are more appropriate and more effective than using point-of-purchase signage to convey a complex consumer message. The program uses health professionals and the media to inform high-risk populations, including women who may become pregnant, pregnant women, nursing mothers and the parents of young children, about mercury in seafood. The goal is to inform these high-risk consumers that they should avoid or restrict their consumption of certain kinds of fish, while emphasizing the importance of fish and shellfish as part of a healthy diet.

The public education campaign includes an extensive outreach effort to over 9,000 print and electronic media outlets. FDA and EPA have also distributed over four million brochures about the advisory on methylmercury in fish and shellfish to members of over 50 organizations of healthcare providers to women and children. The brochures have also been given to all practicing pediatricians, obstetricians, gynecologists, nurse practitioners, and nurse midwives throughout the country for office distribution. And, finally, we distribute it through exhibits at medical and public health professional organization meetings. This information is also available on our Web site for use by States, food facilities, health care professionals, and consumer groups.

In August 2005, FDA launched an educational program entitled "Food Safety Moms-To-Be" that builds upon several food safety messages and includes information for use by health educators about the advisory on methylmercury in fish and shellfish. More than 45,000 Educator Toolkits, including an Educators Resource Guide, video, and DVD were sent to health professionals who have direct contact with pregnant women via pregnancy planning, prenatal and post-natal care, and childbirth education classes.

FDA also established a Web site for pregnant women to obtain information about foodborne safety. The Web site received more than 35,000 visitors in its first full month of September 2005, is available in both English and Spanish, and has an "email a friend" feature that allows users to share this information with others.

FOODNET

Question. The Foodborne Diseases Active Surveillance Network (FoodNet) is the principle foodborne disease component of CDC's Emerging Infections Program (EIP). It is a collaborative project of the CDC, FDA, and USDA. Unlike the direct funding that comes from USDA which has remained consistent, the funds from CDC and FDA are derived from the larger Food Safety Initiative and are thus subject to being reallocated. Over the last 5 years the program has experienced a 10 percent decrease in funding. Cuts to the FoodNet Program will have a direct effect on our Nation's ability to identify and track foodborne illness.

How have these cuts impacted our ability to identify and track foodborne illness?

Answer. FDA has provided a consistent level of funding in support of FoodNet over the years and has experienced no change in the availability of information we need to direct and evaluate the effectiveness of our regulatory programs. FDA will work with the Committee if specific funding information is needed from CDC.

Question. Do you support giving direct line item funding to the FoodNet Program?

Answer. While FDA believes that FoodNet is a valuable tool for identifying and tracking foodborne illness, which allows the agency to evaluate the effectiveness of its regulatory programs, FDA does not support giving direct line item funding to the FoodNet program in the FDA appropriation.

QUESTIONS SUBMITTED BY SENATOR BYRON L. DORGAN

IMPORTED PRESCRIPTION DRUGS

Question. Given the substantial price differences between products sold in the United States and abroad, it should come as no surprise that millions of Americans already import prescription drugs.

How much did the FDA spend in fiscal year 2005 to prevent Americans from importing prescription drugs from Canada and other countries?

Answer. FDA prevents unauthorized importation of drugs from other countries through post-market import inspections and post-market import laboratory analyses. In fiscal year 2005, the Office of Regulatory Affairs spent \$6.4 million on post-

market import inspections and \$1.7 million on post-market import laboratory analyses of human drug imports from all countries. Post-market import inspections are defined as physical inspections, product information, line entry & label review. They include all the activities relating to the decision to permit or refuse entry to regulated products. Examples include: import field exams, import sample collections, Operational and Administrative System for Import Support on-screen reviews, review of physical documents, detention without physical examination, private laboratory report review and audit activities, filer evaluation, and follow up to refusals. Post-market import laboratory analyses are defined as sample analysis, product testing, methods development for testing purposes, specific regulatory problems that FDA develops solutions for. They exclude applied research and premarket review analyses and include fingerprinting.

Question. Much of the apparatus for assuring safe consumer access to imported drugs is already in place. Under current law, drug companies are free to manufacture prescription drugs in other countries and import them for sale in the United States. More than \$40 billion of the prescription drugs consumed by Americans in 2002—one quarter of all drugs—was made in other countries and imported to the United States for sale by pharmaceutical manufacturers.

If importation can be deemed safe for manufacturers, why can't it be made safe for consumers? Wouldn't a regulated system be safer than what is occurring today?

Answer. 21 USC 381(d)(1) was included in the Federal Food, Drug, and Cosmetic Act with the understanding that the manufacturer of a drug product is in the best position to know if a drug product destined for import into the United States is their genuine product, and not a counterfeit, and whether it has been stored or handled in such a way as to affect the integrity of the product. Because counterfeiters are so sophisticated in their methods of copying drug products and packaging, consumers, distributors, and retailers, are not in a position to easily distinguish genuine from counterfeit drug product. Oftentimes, the manufacturer must perform costly and complicated analysis to determine if a product is genuine or not.

The HHS Drug Importation Task Force Report issued in December 2004 outlined the measures that would be needed to implement an importation program that provides adequate safeguards and resources to ensure that the imported drugs are safe and effective. A program that does not take these measures into consideration, regulated or not, would perpetuate the buyer beware situation that is currently occurring and consumers would continue to put themselves at risk for harm by importing unapproved drugs into the United States for personal use.

Specifically, the Task Force made a number of significant findings about an importation program. The Task Force determined that first, integrity of the distribution system must be ensured by, among other measures, requiring drug pedigrees with adequate documentation, limiting ports of entry and distribution channels, and allowing commercial importation only from licensed foreign wholesalers to authorized sellers in the United States. The program must exclude personal shipments via the mail and courier services. Indeed, regulating personal importation could be extraordinarily costly, on the order of \$3 billion a year based on estimates of the current volume.

Second, any program must limit importation to those prescription drugs most likely to yield savings—namely high-volume products for which a United States—approved generic is not available—and allow importation only from countries for which we have a high degree of confidence in the comparability of their drug regulatory systems. In the Administration's view, Canada is the only country from which importation should be considered at this point. Congress should also exclude drugs or classes of drugs that pose increased safety risks in the context of importation, such as controlled substances and drugs that require refrigeration during shipping.

Third, any program must require that imported prescription drugs be dispensed pursuant to a valid U.S. prescription pursuant to advice from a trusted medical professional.

Fourth, measures must be included to ensure that any purchasers of imported drugs are given full and adequate information regarding, among other things, the source of the drugs, and that packaging and labels on imported drugs meet all FDA requirements.

Fifth, any importation program must ensure effective oversight and adequate government resources to protect American consumers.

Sixth, any program must include the ability to use streamlined inspection procedures, and ensure appropriate remedial steps can be taken in the event of adverse events from imported drugs.

Seventh, any program must avoid anti-competitive provisions such as so-called "forced sale" provisions, and other types of price controls.

The Task Force found that such a system would have minimal cost savings.

Question. Congress has twice enacted legislation to allow for the importation of prescription drugs. Both times provisions were included that required the Secretary of Health and Human Services to certify that imported drugs would be safe and would result in significant savings for the American consumer. The Congressional Budget Office has already determined that legalizing importation will reduce prescription drug expenditures by \$50 billion. CBO estimates Federal savings of \$1.6 billion over the 2006–2010 period and \$6.1 billion over the 2006–2015 period. That takes care of the savings argument.

In terms of safety, how do you guarantee the safety of drugs that are sold in the United States? How did the FDA guarantee the safety of Vioxx? Why is the bar set higher for imported drugs?

Answer. At FDA, the Center for Drug Evaluation and Research, or CDER, is responsible for ensuring that America's drug product supply is safe, effective, adequately available, and of the highest quality. CDER's responsibility for ensuring drug safety is two fold, consisting of premarket safety review and postmarket safety surveillance. We evaluate the safety of a drug before it can be marketed in the United States in a pre-market safety review. FDA grants approval to drugs after a sponsor demonstrates that they are safe and effective for their intended use. Since the full magnitude of some potential risks do not always emerge during the mandatory clinical trials conducted before approval to evaluate these products for safety and effectiveness, if CDER approves a drug, we continue to monitor the safety of that drug after it is on the market by collecting data about its use and watching for signs of troubling or dangerous side effects. We call this post-market safety surveillance.

No drug product is "perfectly" safe. Moreover, FDA approval of a drug is not a "guarantee" that the drug is "perfectly" safe. All approved drugs pose some level of risk since every drug that affects the body will have some side effects. FDA considers both the benefits and risks of all medications before approval and unless a new drug's demonstrated benefit outweighs its known risk for an intended population, FDA will not approve the drug. Medications needed to treat very severe or life-threatening illnesses such as cancer treatments may be approved with more serious side effects than other types of medications. FDA makes sure the label or package insert accurately describes the benefits and risks discovered in the clinical trials and after marketing. With the help of a health-care provider, a patient should decide if the benefits for the drug outweigh the risks.

The pre-market process for approving drug products begins with the drug companies who must first test their products. CDER monitors their clinical research to ensure that people who volunteer for studies are protected and that the quality and integrity of scientific data are maintained. CDER assembles a team of physicians, statisticians, chemists, pharmacologists, and other scientists to review the company's data and their proposed use for the drug. If the drug is effective and we are convinced that it is safe for its intended use— meaning that its health benefits outweigh its risks, we approve it for marketing in the United States. CDER does not actually test the drug when we review the company's data. By setting clear standards for the evidence FDA needs to approve a drug, including evidence for demonstrating the safety of the drug for its intended use, the Agency helps medical researchers bring new drugs to American consumers more rapidly.

Once a drug is approved for sale in the United States, FDA monitors the use of marketed drugs for unexpected health risks, either through post-marketing clinical trials or through spontaneous voluntary reporting of adverse events from patients, doctors, and nurses through MedWatch system that are entered into the Adverse Event Reporting System, or AERS. Our safety reviewers monitor the data in AERS looking for indications of potential serious, unrecognized drug-associated reactions. If new, unanticipated risks are detected after approval, we take steps to inform the public and change how a drug is used or even remove a drug from the market.

Following the process and fundamental principles just described, FDA originally approved Vioxx in May 1999 for the reduction of signs and symptoms of osteoarthritis, as well as for acute pain in adults and for the treatment of primary dysmenorrhea. The original safety database included approximately 5,000 patients on Vioxx and did not show an increased risk of heart attack or stroke. A later study, VIGOR, which stands for VIOXX GI Outcomes Research, was primarily designed to look at the effects of Vioxx on GI effects such as stomach ulcers and bleeding and was submitted to the FDA in June 2000. The study showed that patients taking Vioxx had fewer stomach ulcers and bleeding than patients taking naproxen, another NSAID, however, the study also showed a greater number of heart attacks in patients taking Vioxx. The VIGOR study was discussed at a February 2001 Arthritis Advisory Committee and the new safety information regarding all that was known at the time about the potential risk of cardiovascular effects with Vioxx from this

study was added to the labeling for Vioxx in April 2002. Merck then began to conduct longer-term trials to obtain more data on other potential indications of this product. All trials for chronic use were designed to monitor carefully for cardiovascular safety. The serious side effect risks for which Vioxx was ultimately withdrawn from the market voluntarily by Merck were identified when Merck collected new data from a trial called the APPROVe, which stands for Adenomatous Polyp Prevention on VIOXX trial where Vioxx was compared to placebo. The purpose of this new trial was to see if Vioxx 25 mg was effective for a new indication—for preventing the recurrence of colon polyps. This trial was stopped early because there was an increased risk for serious cardiovascular events, such as heart attacks and strokes, first observed after 18 months of continuous treatment with Vioxx compared with placebo.

The bar is not set higher for imported drugs. In fact, the bar is identical to that for FDA-approved drugs. The problem with illegally imported prescription drugs is that we often have no assurance that they have been manufactured, processed and held according to the same requirements and standards as FDA-approved drugs. FDA drug approvals are manufacturer- and product-specific and include many requirements relating to the product, such as manufacturing location, formulation, source and specifications of active ingredients, processing methods, manufacturing controls, packaging location, container/closure system, and appearance (21 CFR 314.50). Frequently, drugs sold outside of the United States are not manufactured or packaged by a firm that has FDA approval for that drug. Moreover, even if the manufacturer has FDA approval for a drug, the version produced for foreign markets may not meet all of the specific requirements of the United States approval, and thus would be considered to be unapproved (section 505 of the Act (21 U.S.C. 355)).

In December 2004, the HHS Drug Importation Task Force Report on Prescription Drug Importation concluded that any safe system of importation would likely produce only modest savings on the national level. The small quantity of available drugs to import would result in little aggregate cost savings. The Task Force included a report with the results from a Department of Commerce study. That study concluded the reduction of research and development of competitive markers for generic medicines, thereby denying consumers in those markets benefits, including lower prices that Americans obtain as result of competition between generic and brand-name drugs. In fact, U.S. consumers would pay, on average, 50 percent more for their generic medications if they bought them abroad.

Question. Mark McClellan has said, “If you’re certain you’re buying approved Canadian drugs from an approved Canadian pharmacy,” he says, “you can have a high level of confidence that that’s a good product.”

If we could figure out a system that makes importing drugs just like walking into a brick and mortar Canadian pharmacy, wouldn’t it be safer than what is occurring today?

Answer. The HHS Drug Importation Task Force Report on Prescription Drug Importation issued in December 2004 outlined measures that would be needed to implement an importation program that provides adequate safeguards and resources to ensure that the imported drugs are safe and effective within the meaning of the Federal Food, Drug, and Cosmetic Act. An importation program that does not take these measures into consideration would frustrate our ability to ensure that the prescription drugs imported for personal use were safe and effective for their labeled uses.

Specifically, the Task Force made a number of significant finding about an importation program. The Task Force determined that first, integrity of the distribution system must be ensured by, among other measures, requiring drug pedigrees with adequate documentation, limiting ports of entry and distribution channels, and allowing commercial importation only from licensed foreign wholesalers to authorized sellers in the United States. The program must exclude personal shipments via the mail and courier services. Indeed, regulating personal importation could be extraordinarily costly, on the order of \$3 billion a year based on estimates of the current volume.

Second, any program must limit importation to those prescription drugs most likely to yield savings—namely high-volume products for which a United States—approved generic is not available—and allow importation only from countries for which we have a high degree of confidence in the comparability of their drug regulatory systems. In the Administration’s view, Canada is the only country from which importation should be considered at this point. Congress should also exclude drugs or classes of drugs that pose increased safety risks in the context of importation, such as controlled substances and drugs that require refrigeration during shipping.

Third, any program must require that imported prescription drugs be dispensed pursuant to a valid U.S. prescription pursuant to advice from a trusted medical professional.

Fourth, measures must be included to ensure that any purchasers of imported drugs are given full and adequate information regarding, among other things, the source of the drugs, and that packaging and labels on imported drugs meet all FDA requirements.

Fifth, any importation program must ensure effective oversight and adequate government resources to protect American consumers.

Sixth, any program must include the ability to use streamlined inspection procedures, and ensure appropriate remedial steps can be taken in the event of adverse events from imported drugs.

Seventh, any program must avoid anti-competitive provisions such as so-called "forced sale" provisions, and other types of price controls.

The Task Force found that such a system would have minimal cost savings.

Question. The FDA claims that more than 10 percent of drugs worldwide are counterfeit.

What is this based on? What is the percentage in the European Union? Canada? Are drugs made in Canada that enter the United States considered counterfeit?

Answer. FDA has not stated that 10 percent of the drugs worldwide are counterfeit. Many sources have attributed FDA with this figure; however, it did not come from FDA. In fact, FDA does not know what the prevalence of counterfeit drugs is globally, in the European Union, EU, or in Canada. Drugs that are made in Canada are not considered counterfeit unless they meet the definition of "counterfeit drug" under 21 U.S.C. 321(g)(2). Rather, virtually all prescription drugs imported into the United States from Canada for personal use violate the Federal Food, Drug, and Cosmetic Act, the Act, because they are unapproved new drugs (section 505 of the Act (21 U.S.C. 355)), labeled incorrectly (sections 502 and 503 of the Act (21 U.S.C. 352 and 353)), dispensed without a valid prescription (section 503(b)(1) of the Act (21 U.S.C. 353(b)), or imported in violation of the Act's "American goods returned" provision (21 U.S.C. § 381(d)(1)). Under the American Goods Returned provision of 801(d)(1), it is illegal for anyone other than the original manufacturer of the drug to import into the United States a prescription drug that was originally manufactured in the United States and sent abroad. Because a consumer is not the manufacturer, they are not permitted to reimport prescription drugs into the United States, even if the drugs were made in the United States. Importing a drug into the United States that does not comply with the labeling and dispensing requirements in the Act and/or is an unapproved new drug is prohibited under section 301(a) and/or (d) of the Act (21 U.S.C. 331(a) and/or (d)).

Question. There have been several recent reports that your agency, along with the Customs and Border Patrol, has increased enforcement efforts to stop prescription drugs from coming into the United States. Did the FDA change its policy?

Answer. FDA's guidance on the personal importation of prescription medicine has not changed. However, we have accommodated CBP's new role in the initial screening of packages containing pharmaceuticals by adjusting the application of our procedures for handling pharmaceutical products shipped through international mail facilities. We anticipate that efficiencies gained as a result of the revised CBP procedures will allow CBP and FDA to screen and process a larger number of packages than in the past.

QUESTIONS SUBMITTED BY SENATOR RICHARD J. DURBIN

DIETARY SUPPLEMENTS

Question. Most dietary supplements provide great health benefits for many Americans. As you know, I have worked for years to ensure that dietary supplements are safe for the public—I hope that the dietary supplement adverse reporting system is enacted in the near future. Clearly, such a system would increase the workload of the FDA, and Congress would need to do its part and provide extra funding for your agency.

In the meantime, please advise the Subcommittee on the timeline to publish the final rule on Good Manufacturing Practices for dietary supplements, which were mandated by Congress 12 years ago and still have yet to be finalized.

Answer. The proposed rule was published March 13, 2003, and included responses to numerous comments received after publication of the advanced notice of proposed rulemaking in 1997. The comment period for the proposed rule was extended until August 2003. We held public stakeholder meetings on April 29, 2003, in College

Park, MD, and on May 6, 2003, in Oakland, CA. We also held a public meeting, via satellite downlink, on May 9, 2003, with viewing sites at our district and regional offices throughout the country. After the comment period closed, we began the process of analyzing the comments submitted to the proposed rule. The issues raised by the comments are complex, legally and substantively, and in some cases, novel. We have expended significant internal resources on reviewing and preparing responses to the comments received. In addition, we have worked to ensure that the goals of Dietary Supplement Health and Education Act are carried out with careful consideration of the impact on the dietary supplement industry. We are working to complete the rulemaking.

WOMEN'S HEALTH

Question. In late August, Dr. Susan Wood, the Assistant FDA Commissioner for Women's Health and Director for the Office of Women's Health, resigned over the Administration's refusal to issue a final decision on the emergency-contraception (Plan B) application. She said, "I can no longer serve as staff when scientific and clinic evidence, fully evaluated and recommended for approval by professional staff here, has been overruled." This decision was contrary to the recommendations of the FDA's advisory commission and its review staff. I requested a GAO study, released in November, which found that the decision process to deny the application "was unusual." It is my understanding that the FDA is currently considering a revised request to make emergency contraception available over the counter to women, but require a prescription for younger girls.

What is the status of this request, and what is the FDA doing to further all aspects of women's health?

Answer. On May 6, 2004, the FDA issued a "Not Approvable" letter to Barr Laboratories, sponsor of a supplemental New Drug Application proposing to make the currently approved Plan B emergency contraception prescription product available as an over-the-counter, or OTC product. After reviewing the supplemental application, FDA concluded that the application could not be approved at that time because adequate data were not provided to support the conclusion that young adolescent women can safely use Plan B for emergency contraception without the professional supervision of a licensed practitioner and a proposal from the sponsor to change the requested indication to allow for marketing of Plan B as a prescription-only product for women under 16 years of age and a nonprescription product for women 16 years and older was incomplete and inadequate for a full review.

The applicant chose to revise its application, and in a July 2004 resubmission, the applicant requested to market Plan B as prescription-only for women under the age of 16 and OTC for women 16 years of age and older. In addition, they proposed an educational program for healthcare providers, pharmacists, and patients.

On August 26, 2005, FDA issued a letter to Duramed Research, the successor to the Barr Laboratories application, in response to their July resubmission. The response concluded that the available scientific data are sufficient to support the safe and effective use of Plan B as an OTC product for women who are 17 years of age and older. However, the Agency stated that it was unable to reach a decision on the approvability of the application because of unresolved issues that relate to whether a drug may be both prescription and OTC, depending on the age of the patient, how an age based distinction could be enforced, and whether Rx and OTC versions of the same active ingredient may be marketed in a single package.

On the same date that FDA issued this letter to Duramed Research, FDA issued an advance notice of proposed rulemaking. This rulemaking requested comment on whether to initiate a rulemaking to codify its interpretation of section 503(b) of the Food, Drug, and Cosmetic Act regarding when an active ingredient may be simultaneously marketed as both a prescription and OTC drug product. The comment period on this notice closed on November 1, 2005, and FDA is currently evaluating those comments.

With regard to your question on what FDA is doing to further women's health, FDA's Office of Women's Health also known as OWH continues to expand patient protection and empower consumers for better health by providing consumer information and funding research. OWH continues its Take Time to Care Campaign, a multi-faceted campaign that focuses on the dissemination of health education materials for consumers through activities and collaborative partnerships. OWH continues its Menopause and Hormones Education Campaign providing clear and useful information to women about the use of hormones during menopause. OWH continues to develop and distribute numerous consumer information fact-sheets about FDA-regulated products for women and their families. OWH consumer information and publications are available in approximately 20 different languages.

OWH funds research projects related to FDA products and relevant to women's health and sex differences. The office funds research projects at FDA and academic institutions that are of regulatory significance to FDA. OWH partners with other HHS organizations to identify gaps in women's health research and to leverage limited funding. The office participates in national medical, scientific, and health care conferences sharing information with consumers about FDA regulated products and participating in scientific discussions and presentations advancing the science related to sex and gender differences.

OWH enhances patient protection and consumer health by maintaining an extensive and current electronic "contact database" used to inform patient advocacy groups, health professionals, national organizations, and large insurance carriers of innovative products approved by FDA and important safety information related to FDA regulated products.

OWH is working to transform systems and infrastructure to support critical agency operations regarding electronic knowledge/information management for an integrative IT environment across FDA Centers. The office is developing a "SMART" document approach for FDA reviewers to enhance review quality and consistency. OWH has been working on a business case plan to better allow for electronically tracking the inclusion of women and sex-specific analyses in studies submitted to FDA.

ADVISORY COMMITTEES

Question. As you know, Congress required FDA to publish a quarterly report on your efforts to find unconflicted scientists for FDA panels. Your first report, published January 2006, gave some raw numbers (over 200 resumes review for a limited number of slots) but did nothing to document any specific efforts to find unconflicted scientists.

What specific steps other than cursory resume reviews have you taken to find scientists to serve on advisory committees this year that don't have conflicts of interest?

Answer. FDA has instituted a number of additional steps this year to find experts with limited or no conflicts of interest to serve on FDA advisory committees and panels. FDA scientific and technical staff and their managers generally identify and contact experts, inviting them to fill vacancies on advisory committees or panels. In the past year, FDA's Advisory Committee and Management Staff in the Commissioner's Office and committee management staff at the Center levels have briefed FDA scientific and technical staff and their managers on the importance of identifying potential committee nominees with limited or no conflicts of interest. In an effort to help identify potential conflicts at the earliest possible stage, staff and management were also advised to consider, to the extent possible, the types of products likely to be discussed at upcoming committee and panel meetings when interviewing candidates about financial holdings and industry relations.

Panel and committee members themselves also identify possible candidates to serve on advisory committees and panels. Current committee and panel members are therefore advised to consider possible conflicts of interest when recommending candidates for participation.

We anticipate that the efforts described above will result in the need for fewer waivers in the future. Because committee and panel vacancies are often filled well ahead of meetings, it can be difficult to identify the relevant sponsors or competing companies, and therefore potential conflicts of interest, during the nomination stage. Importantly, one of the most critical mechanisms for preventing and addressing conflict of interest issues continues to be the rigorous analysis FDA conducts to identify conflicts of interest once we know the context of a committee or panel meeting, as well as the process, guided by both Federal statutes and regulations, for determining whether conflict of interest waivers are appropriate. As we pursue FDA's mission to protect the public health, we strive to fill committee and panel vacancies with qualified experts who satisfy the committee composition requirements set forth by Federal law. Finding experts who have no or limited conflict of interest remains one of multiple considerations in identifying who will fill a committee or panel vacancy.

Question. On January 23, a joint meeting of the FDA's Nonprescription Drug Advisory Committee and the Endocrinologic and Metabolic Drugs Committee met to discuss GlaxoSmithKline's weight loss drug, Orlistat, going over-the-counter. It was eventually approved 11-3. Seven scientists were granted waivers for that meeting, including two who had direct ties to Glaxo.

Do you think that public's faith in this committee's decision is undermined by the fact that so many scientist required waivers of conflicts of interest? Does your staff

have enough resources to conduct adequate background research on potential advisory committee members to find people without such conflicts?

Answer. We believe that several factors should serve to bolster the public's faith in the advisory committee recommendation described above.

First, the conflict of interest waivers were granted in accordance with Federal law. The waivers approved for the meeting described above were granted in compliance with 18 U.S.C. 208(b)(3), 21 U.S.C. 355(n)(4), and the applicable Office of Government Ethics regulations.

Second, information regarding these waivers and the underlying conflicts of interest was made publicly available before the advisory committee meeting, as required by law. Waiver documents and information regarding the nature and magnitude of the underlying conflicts of interest were posted on FDA's Internet page prior to the meeting.

Third, the voting results of this meeting do not suggest a bias resulting from conflicts of interest. Five of the seven waivers were granted for members with minimal interests in competing companies. If financial bias was present, one might expect that the final vote would have been directed against the product under discussion. Instead, a significant majority of the members voted in support of the product. Moreover, as stated in the waiver documents posted online, the two additional waivers were granted to scientists receiving minimal compensation that arguably did not constitute "financial interests" under 18 U.S.C. 208(a). FDA proceeded with waivers for these individuals, however, out of an abundance of caution.

To identify potential conflicts at the earliest possible stage, staff and management are advised to consider, to the extent possible, the types of products likely to be discussed at upcoming committee and panel meetings when interviewing candidates about financial holdings and industry relations. Panel and committee members themselves also identify possible candidates to serve on advisory committees and panels. Current committee and panel members are therefore advised to consider possible conflicts of interest when recommending candidates for participation. We believe these steps are sufficient and adequately resourced.

METHYLMERCURY

Question. It is well known that mercury occurs naturally in the environment and can also be released into the air through pollution. It is well established that exposure to elevated levels of mercury during fetal development can have adverse effects on the developing brain and nervous system that can lead to delayed speech and motor development. For these public health reasons, what else can be done to reduce the amount of mercury in seafood?

Answer. There is no technical process that can remove methylmercury from fish. Therefore, FDA and the Environmental Protection Agency (EPA) have implemented a comprehensive public education campaign through health professionals and the media to inform high-risk populations, including women who may become pregnant, pregnant women, nursing mothers and the parents of young children, about mercury in seafood. The purpose of this campaign is to inform these high-risk consumers that they should avoid or restrict their consumption of certain kinds of fish, while emphasizing the importance of fish and shellfish as part of a healthy diet.

The public education campaign includes an extensive outreach effort to over 9,000 print and electronic media outlets, including magazines about pregnancy and young children. Information has also been sent to members of over 50 organizations of healthcare providers to women and children, such as the American Academy of Pediatrics, the American Academy of Family Physicians, the American College of Obstetricians and Gynecologists, and the American College of Nurse Midwives, directors of the Women, Infants, and Children programs, as well as all local health departments.

In addition, brochures about the methylmercury advisory have been sent to all practicing pediatricians, obstetricians, gynecologists, nurse practitioners, and nurse midwives throughout the country for distribution in their offices. The brochures are accompanied by a letter to the health professional that emphasizes the health benefits of fish. The advisory is also being distributed through exhibits at medical and public health professional organization meetings.

To date, FDA and EPA have distributed over four million brochures. The brochures are currently available in English and Spanish, and will soon be available in Korean, Cambodian, Chinese, Vietnamese, Hmong, and Portuguese. This information is also available on our Web site for use by States, food facilities, health care professionals, and consumer groups.

FDA and EPA will continue to review these recommendations and make adjustments, as needed, so that consumers have access to clear, sound dietary informa-

tion. We recognize that the marketplace often has multiple, and at times confusing or contradictory, messages. FDA will continue to provide a clear channel for public health information concerning methylmercury and other foodborne contaminants.

To reiterate FDA's position, consumers should continue to eat a diet that follows the advice given in the 2005 Dietary Guidelines, including eating a variety of seafood. It is useful to note that data from the National Health and Nutrition Examination Survey, operated by the Centers for Disease Control and Prevention, that measures levels of methylmercury in U.S. women of childbearing age and young children through 5 years of age reveal that the overwhelming majority of both women of childbearing age and young children are exposed to methylmercury at very low levels.

The next phase of our risk management process for methylmercury involves a risk analysis that is examining the likelihood of adverse effects through the range of exposures being experienced by U.S. consumers. This project is also examining the likelihood of health and nutritional benefits from eating fish at various levels of consumption.

Question. You recently met with Dr. David Acheson, Director of Food Safety, regarding the adequacy of the FDA's mercury advisory. Dr. Acheson said that the advisory is geared toward childbearing women and young children and the information is disseminated through healthcare providers. At present levels of mercury in canned light tuna, a child would exceed the recommended maximum level of mercury consumption by eating as few as two sandwiches a week that contain tuna.

What steps can the FDA take to better educate consumers about avoiding excessive mercury intake?

Answer. FDA and the Environmental Protection Agency, also known as the EPA, have implemented a comprehensive public education campaign through health professionals and the media. The campaign is intended to inform high-risk populations. These include women who may become pregnant, pregnant women, nursing mothers and the parents of young children, about mercury in seafood. The purpose of this campaign is to inform these high-risk consumers that they should avoid or restrict their consumption of certain kinds of fish, while emphasizing the importance of fish and shellfish as part of a healthy diet.

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DRUG LABELING

Question. The FDA recently issued a final rule on warning label requirements for prescription drugs. In the proposed rule, which was issued in December of 2000, the FDA stated that the rule would NOT preempt state law. Then, in the final rule, the agency asserts that the rule should be interpreted to preempt state law and state tort liability.

Given that the FDA provided no notice of its intention to preempt state law, how did the FDA comply with the notification and consultation requirements mandated by both the Administrative Procedures Act and an existing Executive Order?

Answer. The Administrative Procedure Act requires the Agency to address the comments it receives in response to proposed rules. The discussion you reference in the preamble to the final rule regarding Federal preemption was written in response to the comments received and merely restates the Agency's longstanding position as articulated in amicus briefs filed in court by the Department of Justice, or 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 Federal Food, Drug, and Cosmetic Act when State requirements cause drug products to be misbranded under Federal law.

Next, you correctly reference the preamble to the proposed rule's statement that it was not intended to preempt state actions. Because the rule itself is about the labeling of prescription drugs and is not a rule regarding preemption, and because the codified language did not expressly propose to preempt state law, FDA included the statement you reference in the proposed rule. However, FDA received comments about the product liability implications of the proposed rule and in responding to those comments, FDA mentioned its view of preemption law as it relates to the Physician Labeling Rule. In fact, the rule itself does not create new preemption law in any way; FDA was simply stating in the preamble what it believes the law already is with regard to implied conflict preemption. In addition, implied conflict preemption works to preempt state law when ever conflict with Federal law arises. The agency need not state in a proposed rule that implied preemption might arise for it to actually do so.

With regard to the Executive Order relating to Federalism, although the preamble to the final rule merely stated the agency's view of current implied conflict preemption law and is not part of the codified portion of the rule, FDA consulted with a variety of State officials and representative organizations that represent State officials and governments on its proposed course of action before the final rule was published. FDA considered their input before proceeding.

Question. The FDA had a long-standing policy of allowing States to implement additional safety requirements that would compliment FDA's rules and regulations. Why did the FDA recently stray from the long-standing policy and assert that any differing state law or requirement should be extinguished in favor of the Federal standards, especially in light of new evidence showing some FDA-approved drugs and medical devices are dangerous?

Answer. All drug products have risks and their FDA-approved labeling is designed to reflect the known risks at any given time. Companies are put in the impossible situation of complying with conflicting Federal and state law when Federal law demands they use approved drug labeling and state law requires different warnings. The preamble language represents FDA's view of preemption law and does not abrogate the State's ability to implement safety requirements. States can do so as long as they do not attempt to impose requirements that conflict with Federal law nor frustrate the purposes of Federal law. In addition, the preamble language reflects FDA's long standing views about Federal preemption law and does not reflect a change in FDA policy.

Question. Unelected Federal agencies like the FDA cannot decide, on their own, to extinguish an entire area of state law without congressional authority. Given that Congress never gave the FDA the authority to wipe out numerous state safety laws and requirements, how does the agency find the authority to assert this position?

Answer. FDA did not decide to extinguish an entire area of state law without congressional authority. The six examples in the preamble describe the types of instances where FDA believes that under the Supremacy Clause of the U.S. Constitution and relevant case law, Federal law trumps state law. For instance, state law can not require a warning that would misbrand the product under the Federal Food, Drug, and Cosmetic Act. Similarly, FDA is the expert agency charged by Congress in evaluating the safety and efficacy of drug products, and implied conflict preemption would arise if a State allowed a product liability suit for failing to warn about a specific risk that FDA excluded from the approved label. Companies could be held

liable under state law where state requirements neither conflict with Federal requirements nor frustrate Federal purposes.

Question. The final rule makes clear the agency's position that even if a drug company failed to warn doctors about a drug's known potential dangers—but the warning label was approved by the FDA—the company would be immune from liability no matter how many patients are injured or killed. In those situations, why shouldn't States be allowed to protect their own citizens and allow consumers to hold these drug companies accountable?

Answer. All drug products carry risk. With regard to safety, FDA attempts to approve drugs that have favorable risk benefit balances, and to approve labeling that accurately reflects the known risks about the product. It is unfortunate that people are injured and killed by drug products, but FDA believes that Federal law mandates what warnings are appropriate in the form of approved drug labeling, and that state law requiring different warnings is trumped by Federal law under the doctrine of implied conflict preemption.

ADDITIONAL SUBMITTED STATEMENT

Senator BENNETT. The subcommittee has received a statement from the Advanced Medical Technology Association which will be inserted in the record at this point.

[The statement follows:]

PREPARED STATEMENT OF THE ADVANCED MEDICAL TECHNOLOGY ASSOCIATION

AdvaMed is pleased to provide this testimony on behalf of our member companies and the patients and health care systems we serve around the world. AdvaMed is the largest medical technology trade association in the world, representing more than 1,300 medical device, diagnostic products and health information systems manufacturers of all sizes. AdvaMed's members manufacture nearly 90 percent of the \$86 billion of health care technology products purchased annually in the United States, and more than 50 percent of the \$220 billion purchased annually around the world. AdvaMed members range from the largest to the smallest medical technology innovators and companies and directly employ about 350,000 workers in the United States. More than 70 percent of our members have less than \$30 million in domestic sales annually.

AdvaMed supports the President's fiscal year 2007 budget request of \$229,334,000 for the Food and Drug Administration's (FDA's) Center for Devices and Radiological Health (CDRH). This inflationary increase amount satisfies the fiscal year 2007 requirements of the Medical Device User Fee and Modernization Act (MDUFMA—Public Law 107-250) and the Medical Device User Fee and Stabilization Act (MDUFSA—Public Law 109-43) and is crucial to ensure patients have timely access to lifesaving and life-enhancing products.

Medical Device User Fees

The increasing number and complexity of medical device submissions have overwhelmed CDRH over the last decade. When MDUFMA was crafted, review times for breakthrough products often exceeded over 400 days, despite a statutory ceiling of 180 days. To address these chronic delays, Congress passed MDUFMA in October of 2002 to supplement FDA's resources and expertise and reduce review times for medical technologies. MDUFMA creates a predictable and adequate funding base for CDRH through a combination of industry-paid user fees and an increase in Congressional funding for the agency. Congress also passed MDUFSA last year to ensure the continuance of this critical program.

Medical technology companies have already paid over \$80 million in user fees and will add more than \$150 million to CDRH resources during the first 5 years of the historic MDUFMA agreement. Although the additional appropriations did not materialize in the first 2 budget years of the MDUFMA agreement, Congress provided the nearly \$26 million requested by the President for fiscal year 2005 and the President's inflationary requested amount for fiscal year 2006. This, along with the fiscal year 2007 request for an inflationary increase, maintains the MDUFMA program.

CDRH must be funded adequately to ensure the goals of MDUFMA are met, maintain the United States' position in the rapidly advancing field of medical technology, and ensure patients' timely access to needed medical breakthroughs. AdvaMed requests that the fiscal year 2006 Agriculture Appropriations bill fully fund CDRH at \$229,334,000 to accomplish these important goals.

Additional Fees and Issues

AdvaMed notes with interest that the President's budget calls for collecting some \$22 million for re-inspection fees. We are interested to learn more about the nature of these fees and to which services currently provided by the FDA they will apply. As was discussed last year during crafting of MDUFSA, we are still working with the FDA to learn how the current device user fees are used and generally have concerns about additional fees being applied without better understanding of their use and reflection of costs for providing the intended services. AdvaMed believes any additional fees must be additive to the baseline and must be associated with clearly identified increased performance to benefit the fee payer above and beyond current performance.

Additionally, AdvaMed is concerned that, as in years past, attempts will be made in the fiscal year 2007 appropriations process to alter FDA policy and procedures related to the regulation of new and existing devices. AdvaMed generally opposes such attempts to alter fundamental FDA regulatory policy for medical devices on appropriations bills. We stand ready to offer our expertise on such matters should the need arise in the coming months.

Background on the Medical Device User Fee Program

America is on the cusp of an unprecedented revolution in medical technology driven by major private and public investments in scientific research and computer technology. Congress has also made a multi-billion dollar commitment to double medical research at NIH and unravel the human genome. Medical technology companies also doubled research and development spending in the decade of the 90's.

The vibrant medical technology sector has driven employment gains and a strong balance of trade much to the benefit of the American patient and economy over the last several years. At the same time, the growing number and complexity of new medical devices throughout the last decade, coupled with a drop in the absolute number of reviewers at CDRH has resulted in severe budget strain and increasing delays in approval of new medical technologies for patients.

Prior to passage of MDUFMA, CDRH faced increasing challenges as a result of dwindling resources and accelerating innovation. Staff levels had dropped by 8 percent between 1995 and 2001. By 2001, the average total review time for premarket approval applications had risen to 411 days, more than twice the statutory review time. An FDA science panel warned at the time that increasingly rapid advances in technology "threaten to overwhelm" CDRH's limited resources.

On October 26, 2002, President Bush signed MDUFMA, which was unanimously passed by Congress, into law to give CDRH additional resources and expertise to help provide timely patient access to new medical technologies. It established an industry-funded user fee program to provide up to \$35 million each year to help the agency meet rigorous new performance goals.

Key regulatory reforms in MDUFMA are designed to:

- Eliminate bureaucratic delays in review of combination products by establishing a new office to oversee these technologies
- Authorize FDA to accredit third-party inspectors to audit medical technology companies with a good track record of compliance;
- Encourage timely, thorough premarket reviews by codifying the PMA "modular review" program and extending the third-party review program for 510(k)s;
- Permit paperless device labeling and electronic facility registration.
- Strengthen FDA regulation of reprocessed disposable devices.

From bioengineered organs and implantable artificial hearts to gene-based diagnostic tests and molecular imaging systems, America's medical technology companies are developing thousands of promising new tests and treatments. AdvaMed believes full implementation of MDUFMA will help ensure these advances reach the millions of patients who need them.

The user fee provisions in the law set fees for premarket approval applications, supplements and 510(k) submissions. Under the original law, these fees, combined with funds from increased appropriations, will provide FDA's device program with more than \$225 million in additional resources over the 5 years of the program. A letter agreement accompanying the bill sets review performance goals for the agency.

To assure that these user fees would have an additive effect on the CDRH budget, MDUFMA requires CDRH receive a \$15 million appropriations increase in each of the first 3 years of the program (fiscal year 2003, fiscal year 2004 and fiscal year 2005) for a total of \$45 million by the end of fiscal year 2005, or the user-fee program terminates in fiscal year 2006. These funds are designed to allow CDRH to upgrade information technology and other infrastructure necessary to carry-out a user-fee program and to meet the performance goals.

MDUFMA passed both houses of Congress on the last day of the regular session in October 2002. Owing to the extremely late timing of MDUFMA passage and a very tight budget climate, MDUFMA funding targets were not met in either of the first 2 years of the MDUFMA agreement. MDUFSA was passed last year to allow the program to continue despite the funding shortages in the early years of the program. MDUFSA also addressed the significant rate of increases in fees paid by industry. As Congress has struggled to provide its funding, industry paid user fees (per submission) that far exceed what was expected by MDUFMA. Increases of 35 percent, 15.7 percent and a projected 20 percent for fiscal year 2006 for individual PMA submissions were troubling to industry, and we appreciate the steps Congress took to limit the rates of increase until the program can be reauthorized in 2007.

To maintain the MDUFMA program and protect investments made by the Agency, American consumers and a leading source of job growth in our economy, we ask Congress to again meet the President's fiscal year 2007 budget request for CDRH.

Conclusion

AdvaMed appreciates the Subcommittee's efforts last year and urges them to continue on this path to fully fund MDUFMA and ready FDA for the coming era of biomedical innovation and patients that await timely access to the coming dramatic breakthroughs in medicine. AdvaMed requests that the fiscal year 2007 Agriculture Appropriations, Rural Development, Food and Drug Administration and Related Agencies bill fully fund CDRH at \$229,334,000 to accomplish these important goals. We have concerns about the inclusion of new fees for the FDA to carry out core mission activities and urge the committee to refrain from altering FDA policy and procedures related to the regulation of new and existing devices in the fiscal year 2007 appropriations process.

AdvaMed thanks the committee for this opportunity to present our views and we look forward to working with you to help prepare FDA for the coming revolution in medical technology.

SUBCOMMITTEE RECESS

Senator BENNETT. Thank you very much.

The subcommittee is recessed.

[Whereupon, at 11:25 a.m., Tuesday, March 14, the subcommittee was recessed, to reconvene subject to the call of the Chair.]