

**Food and Drug Administration
Planned FY 2006 Research,
Demonstration and Evaluation (RD&E) Activities**

Overview

FDA research is unique in the application of basic science to support its practical conclusions about complicated products that have consequences that may be nothing less than life or death. Likewise, FDA conducts applied research necessary to support its regulatory decisions on the public health product it regulates. In FY 2006, the Agency will continue to collaborate with other government agencies, industry, and academia to accomplish its research needs.

FDA reviews and makes decisions regarding new products that are the result of cutting-edge science. These decisions must be credible with our peers and the general public. Not only does our applied research help us obtain this credibility but it also provides useful insights for product developers as to how they can solve important technical problems, and helping to ensure that the FDA has adequate expertise to make appropriate decisions and develop regulatory policies in areas of increasingly complex science.

Given the rapid pace of technological changes used by our industry partners, we must maintain scientific credibility with strong FDA intramural, mission-relevant research programs to give us the tools needed to effectively carry out our public health mission by ensuring that the scientific information needed to perform that mission is available. A strong base of applied, intramural research provides an atmosphere that helps us to recruit and retain a high-quality scientific staff that can conduct science-based reviews. It also creates a platform from which agency staff can interact as respected, knowledgeable, and impartial colleagues with the external scientific community, especially with regulated industries in areas of rapidly advancing science and technology that require the involvement of the extramural community.

Examples of unique aspects of FDA research that result in major public health impacts include:

- Shorten review times – in house, cutting edge expertise reduces the need to postpone decisions until ad-hoc experts can be consulted or advisory committees assembled;
- Increase public confidence in and acceptance of new technologies through improved product safety, thus avoiding setbacks and defusing crises that could cause resistance to develop new technologies;
- Shorten product development times by familiarizing researchers with technologies that can help sponsors design and trouble-shoot assays, and enhance manufacturing processes; and,

- Keep FDA research scientists working at the cutting edge area of field to stay current at a time of rapid and explosive change and development.

FDA research contributes to a strong science base that improves and maintains the safety and effectiveness of regulated products. Applied studies assist in meeting FDA's regulatory mission and set standards for activities that include: laboratory techniques to determine if a drug, device, or biologic are safe and effective; and surveillance for unexpected threats to the public health from foods and medical products. The following briefly explains the planned research, demonstration and evaluation activities in FY 2006.

Research is an integral foundation to FDA's five Strategic Plan priorities:

- Improving FDA's Business Practices
Ensure a world-class professional workforce, effective and efficient operations, and adequate resources to accomplish FDA's mission;
- Using Risk-Based Management Practices
The use of science-based efficient risk management in all Agency regulatory activities, allowing FDA to allocate its limited resources to provide the most health promotion and protection at the least cost for the public;
- Empowering Consumers for Better Health
Enable consumers to make smarter decisions by improving access to information so they can weigh the benefits and risks of using FDA-regulated products;
- Patient and Consumer Protection
Seek continuous improvements in patient and consumer safety by reducing risks associated with FDA-regulated products; and,
- Protecting the Homeland -- Counterterrorism
Strengthen FDA's capability to identify, prepare for, and respond to terrorist threats and incidents.

Protecting and Empowering Specific Populations

Mental Health and Drug Treatment

FDA scientists perform fundamental research to develop and validate quantitative biomarkers of neurotoxicity, which are then used for the comprehensive evaluation of neuroactive chemicals of concern to FDA regulatory centers. Our research program includes the availability of facilities for rodent and non-human primate research that help reduce the risk of extrapolating data across species whenever possible. Collaborative behavioral studies are being conducted in partnership with the Arkansas Children's Hospital.

Realizing the possibilities of the 21st Century Health Care

Organ and Donation Transplantation

FDA's programs are directed to facilitate the safe and effective use of transplantation through the characterization of transplantation quality, purity, safety and efficacy. Specific programs are aimed at defining the assays and methods needed to determine cell and tissue product quality and potency, and to evaluate specific product markers through genomics/proteomics and other technologies that provide predictive information about product efficacy and safety after administration. In addition, methods are evaluated that are used to identify product characteristics that predict success or failure of the transplant.

In addition to the research on transplantation, FDA also has programs related to the evaluation of artificial organs and organ assists. These projects include the evaluation of prosthetic heart valves, ventricular assists, stents, and bypass pumps. Other projects include new intra-ocular lens implants, retinal implants, cochlear and middle ear implants. Much of this research focuses on test method development that examines specific device attributes. Another contribution to this area includes modeling of artificial organs for laboratory investigations of function and biomaterial degradation of materials used in artificial organs.

Patient Safety, Quality, and Reducing Medical Errors

The concern for the safety and efficacy of drugs, biologicals, and devices directs the focus of FDA's research programs. Specific programs include: 1) development and validation of methods and biomarkers to detect drug-induced tissue injury and identify underlying mechanisms; 2) assessment of factors that contribute to variability in pediatric pharmacokinetics and/or pharmacodynamic studies, age-dependent metabolic changes, and developing mathematical models to predict drug transfer from mother's blood to milk to estimate drug exposure in breastfed infants; 3) development, improvement, and standardization of diagnostic tests for transmissible infectious agents in blood vaccines and cell/gene/tissue products; 4) measurement and standardization of potency and predicting adverse reactions to blood-based products; 5) developing potency, purity, and safety tests for prophylactic and therapeutic vaccines and anti-allergenic therapies; 6) evaluation of counterfeit products and product contaminants in a rapid and reliable manner; 7) assessment and management of the risk of vaccine neurotoxicity through the development of preclinical safety tests and post marketing studies for virus vaccines; 8) use of genomics to identify early signs of renal or hepatic failure; 9) improved methods for evaluation of drug-eluting stents and interventional cardiology devices; 10) performing testing of drugs where surveillance is required and, 11) development of performance assessment methodology for state-of-the-art diagnostic imaging system.

Ensuring our Homeland is Prepared to Respond to Health Emergencies

Research on Bioterrorism and Chemical Terrorism

FDA research programs to address bioterrorism issues are primarily focused on food defense, development of safe and effective drug treatments for counterterrorism measures, and research on vaccines and biological products used to prevent infection and treat bone marrow damage.

The priorities of FDA's food defense research program are based on determining the food/agent combinations that are of the highest concern. Mission-critical knowledge gaps are addressed through translational research accomplished through an integrated portfolio of intramural, extramural, and consortia-based (industry and/or academia) programs that address the need to anticipate, prevent, detect, respond, and recover from terrorists' assaults on the food supply. This requires research activities in five areas: (1) knowledge of the behavior of microbiological, chemical, radiological, and biologically-derived toxic agents in priority vulnerable foods during the stages of production, distribution, marketing, and preparation; (2) enhanced information on the susceptibility of the population to microbiological, chemical, radiological, and biologically-derived toxic agents via priority vulnerable foods; (3) identification and/or development of new techniques for "shielding" priority vulnerable foods through the development of new prevention and/or security technologies; (4) development of enhanced sampling and detection methods for priority agents in vulnerable foods including field deployable and in-line sensor-based screening, analytical, and investigational (forensic) technologies; and (5) development of effective methods for ensuring that critical food production and manufacturing infrastructure can be rapidly and effectively decontaminated in event of a terrorist attack. The mission-critical needs require that the research not stop at the generation of new knowledge and technologies, but also include the validation of those approaches under realistic conditions that reflect the diversity of the food industry, and the transfer of that technology to the appropriate sectors of the food industry.

In the development of safe and effective drug treatments as countermeasures, specific research programs include: animal models for systemic anthrax disease and for tularemia; animal studies in post-exposure prophylaxis of anthrax to evaluate the efficacy of antimicrobials appropriate for use in special populations; non-human primate studies to evaluate the efficacy of antimicrobials for pneumonic plague; development of antidotes to treat the effects from nuclear attacks; antidotes to chemical threat agents, such as cyanide; safety of drug countermeasures in special populations (e.g., pediatrics, pregnant women, and the elderly); and long-term safety of drug therapeutics. FDA will continue to participate with CDC in the Post-event Surveillance Working Group to develop processes for the collection of post-event safety and outcome information on products distributed due to a terrorist event. These programs are conducted through a combination of intramural programs and collaborations with DoD, NIH, and CDC.

FDA research on vaccines and biological products include programs supporting the licensure of new-generation smallpox vaccines and anthrax vaccines, new tests to define biomarkers for vaccine efficacy by measuring vaccinia-specific immune responses, rapid and reliable new methods for determining vaccine potency for smallpox. Also included are new methods of evaluating smallpox vaccine safety prior to clinical use, identifying critical components of *Bacillus anthracis* important target treatment of patients suffering from anthrax infection, and information important to support the future development of improved vaccines for anthrax. For other agents, research includes approaches to evaluation of an effective and safe vaccine product for prevention of plague. This involves detecting and identifying the toxin, measuring its potency, and treating its effects. Other research involves developing biomarkers as correlates of immune protection for clinical studies using models for tularemia vaccines and development of multiple approaches for detection and identification of threat agents in low concentrations for medical diagnosis and assessment of product purity, including blood. FDA research also supports evaluating the efficacy and safety of use of licensed products to new medical countermeasure applications, including treatment for plague, and cyanide poisoning.

While the above are FDA's primary focus on bioterrorism, there is an Interagency Agreement with the Federal Aviation Administration for the development of test methods and drafting of voluntary standards for testing effects that emissions from security screening systems may have on medical devices.

Food Safety Research

For food safety, FDA's programs have components involving microbiological and chemical contaminants, biotechnology/allergenicity, seafood, dietary supplements, bacterial/viral pathogens in produce, noroviruses in foodworks, mycotoxins in grains, perchlorate in milk, acrylamide in baked foods, animal drug residues, color additives, and market studies. For the microbiology component, the determination of microbiological risk drives the research program. Included is work in microbial genetics, molecular virology, and the molecular nature of the human pathogens in the food supply combined with the characterization of the food-borne microbial pathogens. All this information is vital to our ability to develop risk assessment models for pathogens such as *Escherichia coli* 0157:H7, *Listeria monocytogenes*, and *Clostridium botulinum*. This work includes intramural and extramural programs and collaborations with the Illinois Institute for Technology, U.S. universities, food industry members, and the Joint Institute for Food Safety and Applied Nutrition. In addition, FDA has a collaborative program with CDC and ten public health laboratories involved in the National Antimicrobial Resistance Monitoring System (NARMS) to develop surveillance data on pathogens found in various foods.

While the above programs relate to the occurrence of selected pathogens in food, FDA also conducts studies on the emergence of antibiotic resistance in food pathogens following the feeding of antibiotics to food-producing animals. These studies investigate

how resistance develops, disseminates, and persists in the animal production environment. These studies include intramural and outside collaborations.

For chemical contaminants, biotechnology/allergenicity, seafood, animal drug residues, dietary supplements, and color additives the programs are focused on the development of detection methods. Examples of analytes used in method detection include pesticides, mycotoxin, dioxins, antibiotics in animal derived food, food allergens and Dry9C protein, bacterial and viral pathogens and toxins in seafood, botanicals, soy isoflavones, trans fatty acids, and confirmation analysis for colors. These programs involve intramural and extramural efforts and collaborations with the Illinois Institute for Technology, the Joint Institute for Food Safety and Applied Nutrition, and the University of Mississippi's National Center for Natural Products Research.

The market studies component of this work involves estimating changes in consumer and producer behavior in response to agency regulations and policies. In addition, the relationship between risk assessment and economic analysis is also explored. The Health and Diet Survey collects information on consumer knowledge, awareness, attitudes, and behaviors related to diet and health issues.

Understanding Health Differences and Disparities – Closing the Gaps

Health Disparities Research

FDA conducts research in health disparities investigating why specific people or groups of people may be prone to beneficial or adverse effects of specific therapies. The agency also studies: adverse events following the use of licensed products or exposure to chemical toxins in foods, drugs, cosmetics, and medical devices; the application of the results of animal testing to predict effects of products on humans; and the development and validation of high tech methods for human diagnostics, clinical trial biomarkers, and product characterization, including purity and potential for cancer risk, e.g. DNA Microarray Technology.

Women's Health Research

Scientific evidence of the importance of sex differences throughout the lifespan is prevalent and impacts the risk-benefit analysis for products regulated by the FDA. The FDA will fund research on how these sex differences influence the prevention, diagnosis, and treatment of many illnesses, such as cardiovascular disease and related conditions, with a goal of decreasing the burden of these diseases in women. Results of these studies will serve as a basis for developing efficient risk management programs. Current research designed to fill the gap in information regarding use of prophylactic and therapeutic agents for counterterrorism in women – including pregnant women and the elderly – will be translated into information for consumers. FDA is developing a system to track relevant information such as the inclusion of women in clinical trials and the analysis of clinical data by sex, age, and ethnicity. This data will be analyzed and used to develop policy and standards for data collection and analysis, clinical trial design, and the dissemination of information regarding the risks associated with use of medical products.

Preventing Disease Illness and Injury

Prevention Research – General

A core component of the regulatory drug review function involves testing and research to develop and evaluate new scientific methods and testing paradigms. FDA develops new analytical methods, conducts research on human tissue metabolism, including human and animal studies relevant to human drug utilization, with a focus on pharmacology and toxicology research to establish the best models and end points for accurately predicting the clinical effects of therapeutics before these products enter into human testing. FDA also conducts intramural and collaborative research to provide a scientific basis for guidance development and regulatory decision making to ensure high standards of product quality and performance.

FDA studies the mechanisms by which various regulated products induce their intended effects, as well as unintended adverse effects. FDA reviews submissions aimed at inhibiting adverse events due to unwanted immune responses, such as autoimmune diseases or rejection of transplanted organs, and aimed at enhancing efficacy through promotion of desired immune responses, such as those responses that fight against infections or cancer. To facilitate review of such immunology-related submissions, FDA investigates the mechanisms by which immune cells are activated, suppressed or channeled.

Experimental and focus group studies use mail-intercept and internet methods to investigate qualified health claims for conventional foods and dietary supplements, the Emord-petitioned health claims for dietary supplements, and the proposed footnote that will accompany the trans fat declaration on the Nutrition Facts Panel. Focus groups will also investigate allergen labeling wording and formats and evaluate a variety of symbols and formats designed to provide consumers with “weight of evidence” information for qualified health claims.

Vaccines are the most cost-effective medical prophylactic treatment available. One serious public health threat, influenza, is caused by an easily communicated virus with ever-changing strains that, over time, may not be susceptible to the influenza vaccines in use. This requires continuing vaccine changes, with corresponding regulatory updates. The most concerning outcome would be a huge shift in influenza strain, rendering the current vaccine of little value and resulting in massive health crisis, known as pandemic influenza. To prepare for possible spread of a very novel strain of influenza virus, FDA research evaluates novel influenza immunization strategies that may confer immunity against large numbers of influenza virus strains.

FDA has an ongoing program to reduce or eliminate the spread of transmissible prions, responsible for Bovine Spongiform Encephalopathy, from cattle to human through medical products and food. Current programs focus on developing detection methods and evaluation of rapid tests for detecting prohibited material in animal feed and for

detecting the presence of prions in medical products such as blood and components used in manufacture of medical products such as vaccines.

Scientific evidence of the importance of sex differences in disease and illness throughout the lifespan is prevalent. However, there is a lack of evidence that explains the impact of these differences on disease prevention, and the impact of sex differences on the safety and efficacy of medical products used to prevent, disease. FDA programs will increase the understanding of gender differences in health and disease prevention and the results of such studies will improve prevention, of disease in women and men. The Agency is continuing development of a system to track demographic information such as the inclusion of women in clinical trials and the analysis of clinical data by sex, age, and ethnicity.

Prevention Research – Disease Specific

Asthma Prevention

Respiratory syncytial virus (RSV) causes severe and potentially life threatening lung disease in infants and small children, but there is currently no vaccine licensed for prevention of RSV. There appears to be an association between RSV infection and the increased risk of asthma developing and concerns have been raised regarding a need to better understand any potential relationship between vaccination for RSV and asthma risk. FDA research evaluates anti-RSV immune response in children infected with RSV that appears to be associated with childhood asthma to better assess the risk associated with RSV vaccines and other RSV immune therapies.

Cancer Prevention

Cancer research is focused on determining the “patient-specific” variability in women associated with reduction in treatment efficacy, such as those at higher risk of recurrence of breast cancer following high-dose radiation and chemotherapy. In addition, FDA research evaluates the “patient-specific” variability in susceptibility to the toxicities associated with specific chemicals (including production of other cancers) using new techniques to assess toxicities and carcinogenic risk.

Cardiovascular Disease Prevention

This component of FDA’s Women’s Health Program is focused on prevention, diagnosis, and treatment.

HIV/AIDS Prevention

FDA’s work on HIV/AIDS focuses on the evaluation and acceptance of vaccines.

Agency Specific Priorities

Orphan Products Development

The goal of the Orphan Products Development (OPD) Grant Program is to encourage clinical development of products for treatment of rare diseases or conditions, affecting fewer than 200,000 persons in the U.S. Products studied include drugs, biologics, medical devices, and medical foods. Grant applications are solicited through a Request for Applications published annually in the Federal Register.

The OPD grant program corresponds with the RCC Research Themes and Priority Research Areas on several fronts. First, with regard to the specific research themes, it allows for research in a variety of areas including disabilities, healthy development of youth, mental health, organ transplantation, infant mortality, infectious diseases, and cancer. Secondly, OPD supported research falls within the following priority areas: Protecting and Empowering Specific Populations, Realizing the Possibilities of 21st Century Health Care, Understanding Health Differences and Disparities—Closing the Gaps, and Preventing Disease, Illness, and Injury. The OPD activities support FDA's mission to promote and protect the public health by helping safe and effective products reach the market in a timely way, and monitoring products for continued safety after they are in use.

FDA Intra-Agency Collaboration

FDA has identified several examples of research that have the potential for further intra-agency collaboration, including:

- Research being conducted at CDC on neural tube defects is closely related to similar studies being conducted on folic acid deficiencies;
- FDA is also establishing a microarray center in collaboration with the University of Arkansas for Medical Science and identified a potential scientific exchange within the Agency;
- FDA has established collaboration with the National Cancer Institute to jointly develop genomics programs for the characterization of cellular therapy products.
- FDA has conducted many studies, under reimbursable agreements, in non-human primates on the behavioral aspects of drugs of abuse, developing a battery of tests that can be used to measure operant behavior. These studies have the potential of complimenting similar studies being conducted at Substance Abuse and Mental Health Services Administration (SAMHSA);
- FDA in conjunction with CDC and several public health laboratories (PHL) have initiated research to determine the prevalence of antimicrobial resistant foodborne pathogens in the U.S. food supply. FDA leads the microbiological and

epidemiological parts of the NARMS-FOODNET retail program where CDC coordinates the PHL activities. Increased cooperation and coordination between FDA and CDC has been instrumental in expanding the NARMS program into a new area (retail meats) and has helped reduce duplication of similar research activities; and,

- FDA food safety and food security activities are highly collaborative within HHS most notably with CDC [e.g., PULSENET and FOODNET surveillance] and NIH [e.g., basic research on antimicrobial resistance, especially among zoonotic microbial pathogens, to assist in risk assessment].

FDA – How to Continue to Ensure Coordination of RD&E Activities

Currently, FDA participates in the RCC as well as other research coordinating groups including:

- DHHS Women’s Health Coordinating Committee, which works to coordinate the women’s health activities within the Department;
- American Council on Health and Science (ACHS)-sponsored CRISP system, a database originally created by NIH but available to all DHHS Agencies. This database allows users to access information regarding research projects conducted throughout the Department;
- FDA engages in the review of scientific literature and participates in numerous science forums, including the NIH Research Festival and the annual FDA Science Forum; and,
- FDA is a key member of the Interagency Coordinating Committee for the validation of alternative methods, which evaluates new testing methodologies and makes recommendations about their suitability for regulatory application. This ensures coordination of scientific acceptance of new methodologies among the fifteen participating U.S. agencies.

FDA will continue to be an active participant in RCC meetings and research reporting, as well as continue participation in other research coordinating groups throughout HHS to better utilize opportunities for coordination of RD&E projects.

FOOD AND DRUG ADMINISTRATION
RD& E Funding by Research Theme ^{1/}
FY 2006
(dollars in thousands)

Research Theme	TOTAL FY 2006
Protecting and Empowering Specific Populations	\$ 8,753
Realizing the Possibilities of 21st Century Health Care	\$ 18,342
Ensuring our Homeland is Prepared to Respond to Health Emergencies	\$ 78,894
Understanding Health Differences and Disparities---Closing the Gaps	\$ 8,484
Preventing Disease, Illness, and Injury	\$ 14,758
Promoting Active Aging and Improving Long-term Care	-
OPDIV/Agency Specific Priorities ^{2/}	\$ 16,982
TOTAL AGENCY RESEARCH FUNDING	\$ 146,213

^{1/} FDA reviews and makes decisions regarding new products that are the result of cutting-edge science. These decisions must be credible, not only with our peers, but also with the general public. Not only does our applied research help us obtain this credibility, but it also has the side benefits of providing useful insights for product developers as to how they can solve important technical problems, and helping to make sure that the Agency has adequate expertise to make appropriate decisions and develop regulatory policies in areas of increasingly complex science.

^{2/} Orphan Products Development includes Orphan Products grants and related Administrative costs.