

## NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH (NCTR)

	FY 2004 Actual	FY 2005 Enacted <sup>1/</sup>	FY 2006 Estimate	Increase or Decrease
<b>Program Level</b>	<b>\$39,869,000</b>	<b>\$40,435,000</b>	<b>\$41,381,000</b>	<b>+\$946,000</b>
<i>Total FTE</i>	207	229	220	-9
<b>Budget Authority</b>	<b>\$39,869,000</b>	<b>\$40,435,000</b>	<b>\$41,381,000</b>	<b>+\$946,000</b>
<i>Food Defense</i>	\$164,000,000	\$1,403,000	\$2,403,000	+\$1,000,000
<i>Administrative Efficiencies</i>	N/A	N/A	-\$54,000	-\$54,000
<i>Total FTE</i>	<b>207</b>	<b>229</b>	<b>220</b>	-9

*Includes structure changes to FDA's budget, which displays GSA and Other Rent and Rent Related Activities in the Program line, and the Office of Regulatory Affairs as its own program. ORA estimates are for information purposes only and are not included in the Center program level total.*

<sup>1/</sup>Contains budget authority rescission of 0.8 percent.

### HISTORICAL FUNDING AND FTE LEVELS

Fiscal Year	Program Level	Budget Authority	User Fees	Program Level FTE
2002 Actual <sup>1/</sup>	\$39,259,000	\$39,259,000	0	221
2003 Actual	\$40,403,000	\$40,403,000	0	226
2004 Enacted	\$39,869,000	\$39,869,000	0	207
2005 Estimate	\$40,435,000	\$40,435,000	0	229
2006 Estimate	\$41,381,000	\$41,381,000	0	220

*Does not contain GSA Rent or Other Rent and Rent Related Activities.*

<sup>1/</sup>Includes FDA's FY 2002 Appropriation and the Counterterrorism Supplemental.

### STATEMENT OF BUDGET REQUEST

The National Center for Toxicological Research (NCTR) is requesting \$41,381,000 to conduct peer-reviewed scientific research that supports and anticipates the FDA's current and future regulatory needs. This involves fundamental and applied research to define biological mechanisms of action underlying the toxicity of FDA-regulated products. This research provides the basis to make sound science-based regulatory decisions, and to promote the public health through its core activities of premarket review and postmarket surveillance to better understand critical biological events in the expression of toxicity and at developing methods to improve assessment of human exposure, susceptibility and risk. These scientific findings are then applied to FDA's pre-market review and product safety assurance effort. The mission of NCTR is to:

- Conduct fundamental and applied research aimed at understanding critical biological events, such as adverse drug reactions and/or antibiotic resistance, to determine how people are adversely affected by exposure to products regulated by FDA;

- Conduct peer-reviewed scientific research that provides the basis for FDA to make sound, science-based regulatory decisions, and to promote the health of the American people through the Agency's core activities of pre-market review and post-market surveillance;
- Develop methods to measure human exposure to products that have been adulterated or to assess effectiveness and/or the safety of a product; and,
- Provide the scientific findings used by the FDA product centers for pre-market application review and product safety assurance to the scientific community for the betterment of public health.

## **PROGRAM DESCRIPTION**

The NCTR conducts basic and applied research specifically designed to define biological mechanisms of action underlying the toxicity of FDA-regulated products. This research is aimed at understanding critical biological events to the exposure of toxins and at developing methods to improve assessment of human exposure, susceptibility, and risk. This is particularly pertinent in supporting FDA's role in developing medical counter-measures and other preparatory efforts for the Department's bioterrorism activities.

All of the research performed at NCTR is targeted to fulfill three program strategic research goals in support of FDA's public health mission:

- *Risk Assessment for Regulated Products* includes the development of new strategies and methods to test/predict toxicity and assess/detect risk for FDA regulated products, both new and on the market - this includes new genetic systems and computer-assisted toxicology for use in application review and development of gene chip and gene array technology;
- *Knowledge Bases that Predict Human Toxicity* requires the development of computer-based systems as knowledge bases, that predict human toxicity to enhance efficiency and effectiveness of premarket reviews; and,
- *Methods for Use in FDA Standard Development and Product Risk Surveillance* is the conduct of fundamental research to understand mechanisms of toxicity, assess new product technology and provide methods for use in FDA standards development and product risk surveillance.

NCTR conducts research that supports the Agency's core mission areas through the dedicated efforts of staff in eight divisions, each of which is committed to the study of biochemical and molecular markers of cancer, nutritional modulation of risk and toxicity, developmental toxicity, neurotoxicity, quantitative risk assessment, transgenics, applied and environmental microbiology, and solid-state toxicity. The divisions work closely in a seamless effort supporting the FDA's mission to bring safe and efficacious products to the market rapidly and to reduce the risk of adverse health effects from products on the market.

### ***Translational Research***

*Research performed by NCTR is “translational” – meaning basic information derived from studies is further modified to apply to a specific question that supports FDA’s public health mission. An example of this is the basic research developed to create a mutant mouse or rat. FDA scientists use this capability and apply it to specific rodent strains to assess the safety of a human or animal drug, or to understand the mechanism of action of a food additive or medical device. Studies include the nature, effects and detection of poisons and the treatment of poisonings—toxicology.*

NCTR is co-located with the Office of Regulatory Affairs’ Arkansas Regional Laboratory (ARL) on a large campus to form the Jefferson Laboratories located in Jefferson, Arkansas, situated near the City of Little Rock, Arkansas. The research work performed by NCTR is conducted in 34 buildings and 4 trailers.

### **PERFORMANCE ANALYSIS**

During the latest completed performance period, (FY 2004), NCTR successfully met all of the targets of its four performance goals. For more detailed explanation of these goals and results, please see their respective section contained in the Detail of Performance Analysis under the Supporting Information tab.

NCTR continues to support the Agency’s counterterrorism efforts by conducting research in the effort to protect the Nation’s food supply from a terrorist’s attack. The Center has set ambitious targets in support of these efforts and in order to achieve these targets adequate funding is required.

#### **Performance Highlight:**

<b>Goal Target</b>	<b>Context</b>	<b>Results</b>
Establish a nutrition program in collaboration with other Centers to address the risk associated with obesity in children, nutrition in pregnant women and poor nutrition in sub-populations; and initiate analysis on samples requiring high levels of containment in an accredited biosafety level 3 facility.	The public health risks and need for biomedical and behavioral research related to nutrition and obesity in children and pregnant women have been outlined in reports issued by the Surgeon General (1988), NAS (1994), IOM/NAS (1997-2004) & working/advisory groups within FDA (2003-2004). Scientists must define associations of childhood obesity and the influences of maternal smoking, exposure to drugs and environmental agents.	Collaborative efforts that support this goal / target include participation on a committee involving CFSAN, CVM, and NCTR. This committee has prepared a white paper entitled, “Filling Critical FDA-Related Food and Nutrition Research Gaps.”

## **RATIONALE FOR BUDGET REQUEST**

The budget request for Budget Authority supports various activities that contribute to the accomplishment of program outputs and performance goals, and presents FDA's justification of base resources and selected FY 2004 accomplishments by strategic goal.

### **PROGRAM RESOURCE CHANGES**

#### **Program Account Restructuring**

##### **Other Rent Related Activities Structure Change**

To provide increased flexibility, eliminate the need for the many reprogramming requests to Congress, place accountability for rental costs within the operating program, and better reflect the total cost of each program, this budget changes the way the Other Rent-Related Activities budget lines are displayed by incorporating these resources into Other Activities program level request.

#### **Budget Authority**

##### **Food Defense: +\$1,000,000**

The additional resources aids NCTR in investigating the possibility of interspecies transfer of resistance mechanisms (including transfer to humans) and to conduct research to facilitate the development of rapid, accurate tests to detect and monitor pathogenic microorganisms in food, food producing animals, and human intestinal microflora, and to develop risk assessment models and techniques through the use of computational science.

##### **Management Savings: - \$54,000 and – 1 FTE**

FDA will reduce spending on administrative and IT activities. Specifically, these reductions are:

- **Administrative Efficiencies: -\$54,000 and -1 FTE**

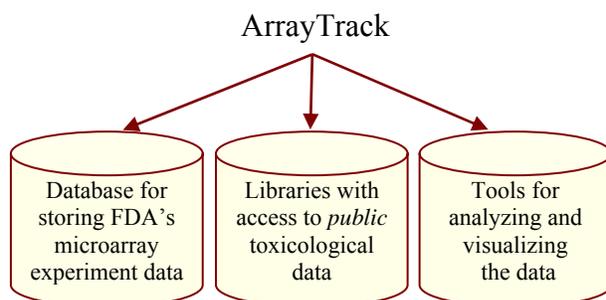
Administrative efficiency savings will total -\$1,554,000 and -15 FTE, of which the NCTR share is -\$54,000 and -1 FTE.

## JUSTIFICATION OF BASE

### USING RISK-BASED MANAGEMENT PRACTICES:

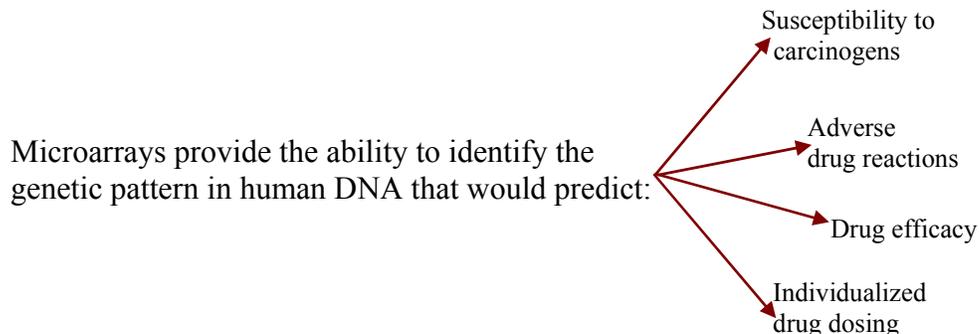
FDA uses science-based risk management in all Agency activities so that limited resources can provide the largest amount of health promotion and protection at the least cost for the public. NCTR's effective risk management efforts:

- Develop a unique and sophisticated analytical infrastructure to assess the safety of FDA-regulated products using genomics, proteomics and metabolomics in conjunction with traditional biomarkers of safety. A systems biology approach to toxicity testing will provide data that are more easily extrapolated to humans, making data interpretation easier and relevant. Scientists believe these developments may prove that new disease markers and drug targets can be identified that will help design products to prevent, diagnose and treat disease;
- Provide software systems and analysis capability to manage and integrate data from new technologies (such as microarrays, proteomics, and functional genomics) with traditional toxicological data. NCTR computational scientists have developed ArrayTrack, a data management and analysis software that is utilized to store and analyze the thousands of data points generated by a single microarray experiment to provide a scientific basis for FDA regulatory standards;



- Use advanced proteomic technology to analyze changes in a given sample after exposure to a toxicant allowing the identification of function and quantification of all proteins in the sample. A mass spectrometer is used to analyze the changes in proteins due to toxicant exposure and to identify possible disease states in the brain, liver, prostate, and blood;
- Develop methods to measure human exposure to adulterated products and enhance the understanding of acute and chronic liver disease. This research is used by FDA's product centers for premarket application review and product safety assurance to improve product quality and better predict the toxicity of new drugs; thereby, managing public health risk;

- Use microchip arrays, small quantities of genetic material bound to computer chips, to analyze a large number of chemical reactions. By using this technique FDA can provide physicians with a means to provide diagnosis and/or treatment to patients more quickly;



- Collaborate with FDA Centers, other agencies and academia to develop a viable nutrition program to improve human health and evaluate the toxicity of botanical ingredients in dietary supplements. These programs, that are of vital interest to the FDA, promote research dealing with chronic obesity in children, nutritional requirements in pregnant women, and nutrition and its linkage to diabetes; and,
- Use chemical probes to determine if bacteria in food and food producing animals or their environment have developed resistance to commonly used antibiotics.

**PATIENT AND CONSUMER PROTECTION:**

Another important function of FDA is to identify risks associated with the use of medical products and reduce the occurrence of adverse events. FDA provides the scientific findings used by its product centers for premarket application review and product safety assurance to the scientific community to promote public health. The Agency develops methods to manage or assess risk associated with products that have been adulterated, intentionally contaminated, or found to be detrimental to human health. NCTR will continue to:

- Investigate the long-term consequences of using HIV therapeutics and endocrine disrupter products particularly from generation to generation;
- Develop animal models with genetic material from other species to better predict how animal study data relate to humans; and,



Simulated  
solar light

- Address the potentially hazardous effects of sunlight with products used by the public. NCTR has one of only two phototoxicology laboratories in the world with the capacity to expose large numbers of animals to simulated solar light – almost any light to which humans are exposed. Studies of particular concern being conducted at NCTR include:
  - Interaction of sunlight and cosmetics;
  - Safety of products (such as dietary supplements, sports drinks, or skin creams) containing aloe vera; and
  - Stability and toxicity of tattoo ink ingredients.

#### ***Toxicant-Induced Exposure***

*Studies are conducted to evaluate tissues and biological fluids for changes in metabolite levels that result from toxicant-induced exposure. This exposure could stem from adulteration of a product through the manufacturing process or as a result of a biological agent.*

### **PROTECTING THE HOMELAND -- COUNTERTERRORISM**

FDA continues to monitor, evaluate, and follow up on the public health needs of new regulated products and to evaluate their use in counterterrorism preparedness and response. These activities support the Department's goals to enhance the ability of the Nation's health care system to effectively respond to bioterrorism and other public health challenges. FDA will continue to:

- Conduct fundamental applied research, including animal and microbial bioterrorism research and analytical studies aimed at understanding critical biological events to determine how people are adversely affected by exposure to FDA-regulated products and to develop a means by which potential biowarfare agents can be rapidly detected;
- Conduct research studies of bacterial strains in order to respond rapidly to various types of emergencies by supporting the rapid detection and identification of biological warfare agents or foodborne contaminants through methods developed in a state-of-the-art Biosafety Level-3 laboratory facility located in Jefferson, Arkansas;
- Conduct studies, developing methods and recommending industry guidelines to evaluate the safety of antimicrobial agents for human health risks. Studies of emerging interest to the FDA under the food security/counter terrorism initiative continuing at NCTR include:

- Human flora-associated mouse model and *in vitro* cell-culture model evaluations of antimicrobial drug residue effects on colonization resistance and host immunity; and,
- Development of a DNA microarray method for the detection of intestinal bacterial species and foodborne pathogens in human fecal samples to monitor drug-mediated perturbations in these indigenous populations.



**In vitro culture system of human colon**

### ***Antimicrobial Resistance***

*Determining limits on antimicrobial residue daily intake for Decision Tree developed at NCTR was adopted into policy, CVM Guidance for Industry # 52 “Assessment of the effects of antimicrobial drug residues from food of animal origin in the human intestinal flora.”*

### **IMPROVING FDA’S BUSINESS PRACTICES**

In support of the strategic goal to foster a strong FDA through scientific recruitments and administrative efficiencies, NCTR has increased its scientific expertise in the areas of computational science, food safety and counterterrorism by hiring additional expertise in these areas. NCTR has actively participated in the development of the Shared Services Organization designed to provide customer-centric administrative services agency-wide resulting in administrative efficiencies. To achieve this goal, NCTR transferred approximately 50 percent of its administrative staff to shared services and has downsized the remaining administrative staff by 13 percent. In addition, NCTR staff received the *Presidential Award for Leadership in Federal Energy Management* for reducing energy consumption by 37 percent over a 10 year period in support of Executive Order 13123. This happened by establishing an agreement with Entergy Arkansas to provide energy management projects.

By improving its business practices, FDA will ensure a world-class professional workforce, effective and efficient operations, and adequate resources to accomplish the Agency’s mission. In support of this goal, NCTR will continue to:

- Reward and retain state-of-the-art scientists and health professionals and utilize web-based recruiting strategies to broaden reach and accelerate access;
- Increase the use of existing formal and informal training programs such as intern programs and mentorship experiences to train and develop a highly skilled workforce;
- Assure that scientists maintain state-of-the-art expertise by training them in emerging technologies; and,

- Support the PMA and FDA's competitive sourcing A-76 effort by performing cost comparison studies for commercially identified functions.

## **SELECTED FY 2004 ACCOMPLISHMENTS**

### **USING RISK-BASED MANAGEMENT PRACTICES**

#### **Toxicological Research**

- Continued development of secure online database technology, known as ArrayTrack, for interpretation of data received from DNA chromosome test studies. ArrayTrack is an integrated software package that plays a critical role in managing, analyzing and interpreting microarray data to study toxicology in human drug and food programs;
- Continued the development of novel computer based predictive tools for the classification and evaluation of chemical toxicity. This toxicoinformatics research is an integrated system of databases, libraries, and analytical to be used in the regulatory review process for chemicals that lack sufficient toxicity data;
- Conducted studies that demonstrate the potential utility of new DNA technology in evaluating the mechanisms by which chemicals exert their toxicity using test methods that sift through and analyze information contained within a set of chromosomes; and,m
- Continued leveraging the Center's limited resources through collaborative efforts to demonstrate the effectiveness of neuroimaging strategies, using non-invasive technology that can be applied both in animal models, and humans, to evaluate various developmental and degenerative dysfunctions including cancer and non-cancer endpoints.

#### **Minority Health**

- Developed mechanisms of neurotoxicity studies to identify gene expression profiles associated with aging and mitochondrial dysfunction. Mitochondrial dysfunction is a common mechanism for neurotoxicity;
- Continued collaborative studies to investigate the association between human genetic variations (polymorphisms) and the risk of breast, prostate, and colorectal cancer; and the influence of polymorphisms on rates of chemotherapy toxicity and cancer survival; and
- Continued genomics research that provides new knowledge on the identification of human subpopulations that are more susceptible to effects of chemical carcinogens, and those likely to experience adverse drug reactions or experience decreased therapeutic drug efficacy.

### **Antimicrobial Resistance**

- Continued to conduct studies on whether new strains of antibiotic resistant bacteria arise from animal feed diets containing antimicrobials; the patterns of resistance developing in these animals and differences in survival rates of antimicrobial-resistant pathogens compared to non-resistant pathogens in the environment; and,
- Conducted microbiological experiments that suggest a technique to reduce or eliminate contamination and survival in the agricultural environment of clinically important antimicrobial drugs.

### **EMPOWERING CONSUMERS FOR BETTER HEALTH**

- Continued writing and developing readership for the ‘Regulatory Research Perspectives’, an online journal with articles of common interest. A recent article on focused the potential unified relationship between (dietary) methyl group insufficiencies and pathologies such as cancer, birth defects, and neurotoxicity. This journal is a vehicle for all FDA scientists to share research advances; and,
- Promoted FDA’s outreach program by disbursing information to the public using informational tools including the annual NCTR Research Accomplishments and Plans document, NCTR Web Page, NCTR One-Pager, NCTR Quarter Page, Center-Wide newsletter, community impact flash presentations, and presentations at scientific conferences and symposia.

### **PATIENT AND CONSUMER PROTECTION**

- Conducted genomic studies to determine the role of skin microflora in the metabolism of tattoo dyes. These studies include evaluating the pigment and topically applied colorants by the skin and intestinal microflora for producing chemical that are toxic to humans; and
- Continued advanced proteomic studies to developing a new and more effective identification, prevention and treatment of *staphylococcal* pneumonia.

### **Dietary Supplements**

- Continued studies on how naturally-occurring toxins contained in, or resulting from, natural products used as food additives and biological therapies, may induce birth defects. This research supports the common theory that diet plays a role in the normal growth and development of normal offspring, and interactions between diet and toxicants may be important in producing certain birth defects.

### **Cosmetics**

- Continued studies to measure the effect of cosmetic ingredients on sunlight-induced skin cancer, and the toxicity of tattoo ink ingredients interacting with sunlight, including those used in permanent make up. These studies are conducted in the unique state-of-the-art phototoxicology facilities and are timely, given the large numbers of young Americans receiving tattoos; and
- Began development of an experimental transgenic mouse model to study melanoma of the skin. An important finding concerning this model has been the occurrence of spontaneous ocular melanoma.

### **Women's Health**

- Continued studies investigating whether the agent genistein (a naturally-occurring plant hormone and dietary supplement) can decrease the induction of carcinogen-caused mutations;
- Continued a collaborative project on investigating the influence of biotin on the developing rat embryo; and
- Conducted experiments on the potential toxicity of the-antiestrogen tamoxifen, a drug being used as a chemoprotective agent against breast cancer.

### **Drug Safety**

- Continued developing and validating new methods that can be used for the identification of potentially hazardous food additives, human and animal drugs, biological therapies and medical devices;
- Evaluated AIDS therapeutic drugs (zidovudine and lamivudine) and the dietary supplement bitter orange regarding their carcinogenicity as well as measuring other endpoints to determine the mechanisms for the adverse effects of the chemicals; and
- Continued studies that measure the neurochemical and behavioral alterations associated with depression risk and Accutane therapy.

### **Children's Health**

- Assessed the potential public health risk associated with the use of anesthetic agents that are known to interact with the neuro-receptor systems of children which has become a growing health concern, particularly as affected in combination with drugs and other environmental agents;

- Conducted collaborative experiments to evaluate ketamine administration and brain growth spurt and rates of nerve ending death; and
- Continued studies that examine the performance on a variety of behavioral tasks that measure complex brain functions in pre-adolescent children diagnosed with major depression.

### **Nutrition**

- Experiments continued on the food contaminant acrylamide, a known animal carcinogen that develops in foods with high starch content and prepared at high temperature, (e.g., potato chips, crackers, cereal, etc.). These investigations emphasize dose-response relationships of toxicity and the development of biomarkers for assessing exposure. Data supports a mechanism how acrylamide becomes a genotoxic carcinogen;
- Continued studies of nutritional folic acid deficiency and tumor progression in newborns; and developed analytical methods for the extraction and determination of chemicals found in dietary supplements and various functional foods; and
- Studied continued on the impact of dietary restrictions and the positive effects for the overall health. These types of studies increase the knowledge of how calories modify the mechanism underlying cancer development in humans and reducing the incidence of these diseases.

### **PROTECTING THE HOMELAND – COUNTERTERRORISM**

- Developed a rapid, reliable, and cost-effective mass spectrometric method to identify pathogenic agents to the strain level. These methods utilize pattern recognition-based methods to differentiate harmless materials from hoax counter terrorism materials;
- Continued collaboration with the ARL to develop microbial isolation procedures that dramatically reduces analysis time of contaminated food;
- Continued methods development to expand the food decomposition gas release methodology to detect explosives in airline cargo; and developed a novel nanoparticle based filter technology to protect the public from chemical and biological contaminants; and
- Continued sharing expertise and laboratory infrastructure to prevent or minimize threats by leveraging the Center's limited resources through a memorandum of agreement with the Arkansas Department of Health.

### Program Activity Data

<b>PROGRAM WORKLOAD AND OUTPUTS</b>	<b>FY 2004 Actuals</b>	<b>FY 2005 Estimate</b>	<b>FY 2006 Planning Level</b>
Research Publications	184	200	200
Scientific Presentations	315	315	315
Patents (Industry)	5	5	5
Interagency Agreements	6	5	5
Cooperative Research & Development Agreements	4	7	7
Total Active Research Projects	194	205	205

## Performance Goals and FY 2006 Targets

The following table of performance goals and FY 2006 targets is presented to compliment the sequential display of this program's "outputs" by more closely linking the traditional budget presentation of base and increased activities and workload outputs contained in the Program Activity Data (PAD) charts. Activities discussed throughout this narrative support the accomplishment of outputs (PAD and performance goals) which in turn contribute to the accomplishment of long term outcome and strategic goals. Full cost information for these goals as well as other historical information has been provided in their respective sections in the Detail of Performance Analysis contained in the supporting information tab.

Performance Goals	Targets
<b>1. Use new technologies (toxicoinformatics, proteomics, metabolomics, and genomics) to study the risk associated with how an FDA-regulated compound or product interacts with the human body. (16014)</b>	FY 06: Present one finding utilizing novel technologies to assess changes in genes and pathology, and the relationship between chemical exposure, toxicity and disease.
<b>2. Develop computer-based models and infrastructure to predict the health risk of biologically active products. (16003)</b>	FY 06: Interpret at least one toxicology study at the molecular level utilizing the DNA microarray database (ArrayTrack).
<b>3. Develop risk assessment methods and build biological dose-response models in support of Food Security. (16007)</b>	FY 06: Demonstrate one utility of an oligonucleotide-microarray method as an integrated strategy to respond to antibiotic resistant agents in foodborne pathogens and bioterror agents.
<b>4. Catalogue biomarkers and develop standards to establish risk in a bioterrorism environment. (16012)</b>	FY 06: Present one finding utilizing neuropathology and behavioral risk evaluation in the prediction of human outcome to food-borne toxicants.