NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

The FY 2009 program level budget request for the FDA's National Center for Toxicological Research is $45,816,000.

The following table shows a three-year funding history for the National Center for Toxicological Research:

FDA Program Resources Table

	FY 2007 Actual	FY 2008 Enacted	FY 2009 Estimate	FY 2009 +/- FY 2008
Program Level	**$42,056,000**	**$44,006,000**	**$45,816,000**	**$1,810,000**
Center	*$42,056,000*	*$44,006,000*	*$45,816,000*	*$1,810,000*
FTE	*183*	*190*	*190*	*0*
Program Level FTE	**183**	**190**	**190**	**0**
Budget Authority	**$42,056,000**	**$44,006,000**	**$45,816,000**	**$1,810,000**
Center	*$42,056,000*	*$44,006,000*	*$45,816,000*	*$1,810,000*
Food Protection (non-add)			*$1,733,000*	*$1,733,000*
Med. Prod. Safety & Devel. (non-add)			*$388,000*	*$388,000*
Admin. Savings & Man. Efficiencies (non-add)			*-$311,000*	*-$311,000*
Budget Authority FTE	183	190	190	0

The FDA's National Center for Toxicological Research operates under the following legal authorities:

Federal Food, Drug, and Cosmetic Act [21 U.S.C. 393(b) (1)]
Food and Drug Administration Modernization Act*
Food and Drug Administration Amendments Act of 2007*

Allocation Method: Direct Federal/Intramural

* Authorities under this act do not appear in sequence in the U.S. Code. The authorities are codified as amended in scattered sections of 21 U.S.C.

Program Description and Accomplishments

The FDA's National Center for Toxicological Research (NCTR) conducts peer-reviewed scientific research and provides expert technical advice and training that enables FDA to make sound science-based regulatory decisions that improve the health of Americans. The research conducted by the National Center for Toxicological Research provides cutting-edge technology for FDA reviewers and solutions to complex safety issues by closing the gap between discovery and practical application in determining the safety of products for patient use.

NCTR receives federal appropriations to execute its mission under the legal authorities highlighted above. NCTR spends all of its resources to conduct scientific research in support of the FDA's mission to bring safe and efficacious products to market and to reduce the risk of adverse health effects.

NCTR was established in 1971 as a national scientific resource to conduct research that translates knowledge and technology into processes that improve the safety-assessment of FDA-regulated products. Through the efforts of highly trained scientists and contract support staff, NCTR conducts fundamental and innovative laboratory research vital to FDA's mission of protecting public health.

NCTR leads national and international collaborations and innovation among government, industry, and academic partners to leverage resources to address regulatory review needs, develop solutions to complex safety issues, and promote the international standardization and global harmonization of regulatory science.

NCTR executes its research responsibilities in three program areas: Personalized Nutrition and Medicine, Food Protection, and Enhancing Product Safety.

<u>Personalized Nutrition and Medicine</u>

Under Personalized Nutrition and Medicine, NCTR aims to define and characterize individual responses to regulated products and to assess innovative products for possible uses. Personalized Nutrition and Medicine utilizes modern innovative technologies and designs new approaches to identify persons most likely to benefit from, or experience adverse reactions to, particular drugs, devices, biologics, cosmetics, and nutrients. Development of science-based individualized treatment therapies will increase treatment effectiveness and reduce the rate of adverse events in patients. Personalization is aimed at changing the public's perception that there are good drugs and bad drugs, to a more accurate impression that certain drugs may work well for certain people, but poorly for others.

NCTR promotes Personalized Nutrition and Medicine by developing a broad range of studies involving systems toxicology assessments to characterize biomarkers of health, disease risk, and disease status. These biomarkers will aid the FDA in assessing the benefits and potential risk of treatments in a personalized nutrition and medicine paradigm. NCTR will explore new approaches such as nutrigenomics to better understand how individual attributes affect responses to drugs, foods, nutrients, dietary supplements and their interactions with toxins and drugs.

Under Personalized Nutrition and Medicine, NCTR supports the Department of Health and Human Services (DHHS) priority of *Personalized Health Care* and FDA's *Critical Path to Personalized Medicine*. Under these programs, DHHS anticipates being able to dramatically increase the success rate in providing patients with innovative solutions that strike an optimal balance of high benefit and low risk because they are "personalized;" making the goal of reducing the pain, suffering, and cost to patients and the health-care system that result from avoidable drug side-effects more achievable.

NCTR conducts regulatory research to support Personalized Nutrition and Medicine with collaborations in the systems biology realm of research with industry, academia, and within FDA, and has identified a performance outcome related to personalized medicine. NCTR's overall performance to date for FY 2004 through FY 2007, combined with FY 2008 goals, indicates NCTR is meeting or exceeding most personalized nutrition and medicine targets. NCTR research is developing classification algorithms for predicting disease and health and is developing a statistical method to identify gender-based biomarkers for both toxicity and efficacy of treatments. NCTR accomplishments in FY 2007 support the goal of personalizing nutrition and medicine.

In FY 2007, NCTR developed a statistical algorithm to classify individual patients into risk/benefit categories for personalized medicine applications. If not carefully considered, analysis of high-dimensional data can easily generate models that do not predict the correct treatment strategies. The newly developed algorithm was used to analyze genomic data sets obtained from lymphoma patients and lung-cancer patients to distinguish disease subtypes for optimal treatment. Additionally, it was used to analyze genomic data obtained from breast-cancer patients to identify those patients most likely to benefit from adjuvant chemotherapy after surgery. The performance of the proposed algorithm consistently ranks high in comparison to other classification algorithms. A description of this algorithm has been published in the journal, *Artificial Intelligence in Medicine* (Vol. 41, pp. 197–297, 2007).

In FY 2007, NCTR identified gender differences in hepatic gene expressions in human liver tissues to further understand the mechanisms of different effects in men and women in drug treatments. This offers the hope of developing recommendations for gender-specific drug development and application. In addition, in FY 2007, NCTR evaluated metabolites in urine samples from three separate studies conducted at CDER to investigate age-related differences in susceptibility to toxicity especially in terms of susceptibility in the pediatric population. The metabolomics result showed that an increase in urinary glucose was a biomarker for liver toxicity. Research results such as these enable scientists to develop safer and more effective therapies that replace one-size-fits-all drugs with treatments that focus on specific population needs.

In FY 2007, NCTR tested the feasibility of using systems biology (global view of biological systems that take into account complex interactions of gene, protein, and cell elements) in the drug-review process by integrating the widely used JMP® Genomics software, which provides powerful data visualization and statistical analysis desktop capabilities, with the FDA genomic tool ArrayTrack™. The new integrated module allows reviewers and scientists to toggle between both software platforms to access the analysis functions available from both software

platforms for review and analysis of pharmacogenomics (the general study of all of the many different genes that determine drug behavior) data.

Food Protection

In support of Food Protection, the public health goals of the NCTR are prevention and intervention. NCTR's Food Protection program will provide techniques to *prevent* food contamination of the food supply or the environment and to ensure timely *intervention* strategies by developing rapid, field-ready standards for the early detection of microbial or chemical threats to the food supply. New methods and risk-based techniques continue to be developed to identify naturally occurring and intentional contamination of the food supply or the environment. To do this, NCTR is expanding the capability to identify, assess, rapidly respond, and reduce food-related health threats.

NCTR develops methods to assess and manage risks associated with food products that have been adulterated, intentionally contaminated, or otherwise found to be detrimental to human health by enabling FDA and other agencies to:

- rapidly determine the source of the contaminant by providing genomic information to the traceback investigation
- closely monitor imported food products contaminated with traditional and non-traditional biological agents that have the potential to cause outbreaks in the U.S.
- more quickly issue health alerts to the state and local public-health agencies in case of an outbreak associated with consumption of contaminated food products
- improve modeling of risk assessment data in present and future food imports.

Under the Food Protection program, NCTR addresses the DHHS goal to enhance the ability of the nation's health-care system to respond to bioterrorism and other public health challenges. The program is also directly linked to one of FDA's Key Initiatives – the *Food Protection Plan*. Through food protection research, NCTR will continue to develop the tools and science necessary to better understand the location of food security vulnerabilities and the most effective ways to minimize them.

The NCTR conducts Food Protection regulatory research in collaboration with industry, academia, and within FDA, and has identified a performance outcome related to food protection. NCTR's overall performance to date for FY 2004 through FY 2007, combined with FY 2008 goals, indicates NCTR is meeting or exceeding most food-protection targets. NCTR research will lead to the development of methods or strategies to: 1) rapidly distinguish bioterror hoax material in samples containing pathogenic and nonpathogenic bacteria, 2) use microarray technology to quickly and inexpensively detect antibiotic resistance markers in *Salmonella* and *E-coli 157:H7*, and 3) reduce the frequency of multidrug-resistant microorganisms and key pathogens in the U.S. food supply. The research conducted by the NCTR in FY 2007 demonstrates scientific contributions to increasing food safety for the public.

In FY 2007, NCTR incorporated flow cytometry technology into regulatory procedures to rapidly detect terror agents. Flow cytometry methods and associated kits have been developed and commercialized via a Cooperative Research and Development Agreement (CRADA)

partner. Assays (methods developed to analyze or quantify a substance) have been developed for three foodborne pathogens (*Salmonella* spp., *Listeria* spp., and *E. coli* general) and are now beginning validation. These methods are being extended: 1) to more dangerous foodborne pathogens like *E. coli O157*, 2) into clinical contexts for the detection of tuberculosis (TB), multi-resistant TB, methicillin-resistant *Staphylococcus aureus*, and vanocomycin-resistant *enterococci*, and 3) into counterterror contexts for the detection of *Bacillus anthracis*, tularemia agent, and *Clostridium botulinum*.

In FY 2007, NCTR and CFSAN researchers co-developed a DNA microarray chip that can accurately process a large number of samples for threat assessment of disease-causing potential during inadvertent or intentional *Salmonella* food contaminations. The technology evaluates 71 of the most common extremely harmful genes that play a significant role in *Salmonella* pathogenicity (its ability to cause disease). The chip has been used successfully for threat assessment of *Salmonella* types isolated from pre-harvest poultry sources and Roma tomatoes. The technique continues to undergo intensive "ruggedness" testing for different field applications. Rapid and cost effective threat assessment of *Salmonella* pathogenicity will be critical to first responders in limiting the potential of accidental or bioterror-related contaminations.

In FY 2007, NCTR scientists, in collaboration with scientists from ORA and CVM, isolated tetracycline-resistant *Aeromonas* and *Citrobacter* spp. from imported aquaculture fish samples. The research data indicated that farm-raised catfish could serve as a reservoir of antimicrobial resistance genes with the potential to transfer drug resistance to the consumer. Another research project, conducted in collaboration with scientists from the ORA Pacific Regional Laboratory, indicated that antimicrobial resistant *Salmonella enterica* serovars were present in imported seafood samples. The molecular techniques developed during the investigation will be used to monitor the nation's food supply for microbial pathogens, which will enhance epidemiological investigations of outbreaks.

Enhancing Product Safety

Under Enhancing Product Safety, NCTR scientists conduct customized bioassessments of regulated products. The goals of Enhancing Product Safety are: 1) to translate toxicity data into a comprehensive risk-based evaluation and 2) to develop reliable and reproducible techniques for conducting safety assessments of FDA-regulated products. Quantitative evaluation of animal data is extrapolated to humans to establish a safety assessment for regulated products. These studies bridge the gap between the laboratory studies and practical application, leverage new technologies, and support collaboration with industry and academia to speed and strengthen the process of regulatory decision-making while increasing confidence and predictability.

Under Enhancing Product Safety, NCTR supports the Department of Health and Human Services priorities of *Transforming the Healthcare System* and *Advancing Medical Research.* The primary objective of Enhancing Product Safety is to decrease the uncertainty, time, and expense of product development. Under the priorities of *Transforming the Healthcare System* and *Advancing Medical Research*, DHHS strives to rapidly approve safe new drugs and devices, while continually monitoring drug and device safety after approval.

NCTR conducts regulatory research in support of Enhancing Product Safety to expand the integration of animal and human data in providing improved risk assessment and has identified a performance outcome related to enhancing product safety. This supports the critical-path initiative of establishing new scientific tools, especially in the area of bioinformatics, to employ a lifecycle approach to product safety. NCTR's overall performance to date for FY 2004 through FY 2007, combined with FY 2008 goals, indicates NCTR is meeting or exceeding most targets towards enhancing product safety. NCTR research will allow FDA to increase the number of safe and effective new products available to the public by integrating new technology and standards into the review and evaluation of FDA-regulated products at all stages of the product lifecycle.
NCTR accomplishments in FY 2007 support the goal of enhancing product safety.

In support of Enhancing Product Safety, the NCTR is conducting ongoing research on pediatric anesthetics, in collaboration with CDER, to explore the nature of ketamine-induced neuronal cell death observed in the developing nonhuman primate, an animal model closely related to the human infant. Control and ketamine-treated animals are being assessed using histochemical, functional, genomic, and proteomic approaches to determine the level of safety during all stages of pregnancy and early childhood; the relationship of dose-level and anesthesia duration to cell death; and the permanency of damage to brain cells. Additionally, a lifetime (2 year) acrylamide-exposure study in rodents is well underway and preliminary data from that study can be found in an abstract and a manuscript. The results from these studies are not only providing fundamental insight into normal developmental processes, but are also providing important data to guide pre- and post-market regulatory decisions and guidance for future preclinical and clinical studies.

Additional work conducted under this program in collaboration with the University of Missouri resulted in the release of user-friendly, Windows®-based software called PostNatal to facilitate rapid testing of different models of metabolism and disposition of drugs against experimental data. The PostNatal program originally was a general platform to investigate physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) parameters of any chemical during postnatal development. PostNatal has evolved to a package of four PBPK programs that can act independently, or can be totally integrated with each other, and is capable of describing complex scenarios of drug metabolism and disposition in adult mice, rats, dogs, and humans. The integration also permits unusual flexibility in the kinds of studies that can be simulated. The ability to simulate drug metabolism and disposition assists in the identification of therapies more likely to be successful with fewer adverse effects and aids the development of guidance for pre-clinical and clinical studies ultimately leading to a reduction in the time and expense of drug development.

In drug development, predicting potential drug-induced liver toxicity—one of the most common causes for the recall of drugs that have been approved by the FDA for use in humans—is critical to enhancing product safety in the drug-approval process. Pre-clinical (animal) studies are used to determine if drugs may be toxic, and the liver is a major target organ of early screening efforts in the pharmaceutical industry. In spite of this, there have been a number of instances in which drugs that gave no indication of liver toxicity in preclinical studies turned out to be toxic to the liver after being approved for marketing. The goal of a Cooperative Research and Development

Agreement (CRADA) initiated by NCTR with BG Medicine in FY 2007 is to create new tools, known as molecular biomarkers, which can be used in preclinical and clinical studies to predict potential liver toxicity in humans.

Humans may also be at risk from exposure to nanomaterials. It is important for FDA to understand the toxicological consequences of the administration of nanoscale drugs, intentional exposure to nanoscale devices, and unintended exposure to nanoscale materials. In FY 2007, NCTR initiated research to increase the understanding of the uptake and toxicity of nanomaterials and their biological impact on the neurological system. Improved understanding of nanomaterials, their transport, and their toxicity will provide a framework for regulatory guidelines for safe and effective use of nanomaterials in FDA-regulated foods, cosmetics, and medical products and provide early recognition of potential safety issues before they become adverse events in the patient population. It is anticipated that NCTR's nanotechnology research program will expand as the number of nanoscale products the regulated community seeks to market increases.

In FY 2007, NCTR conducted training for CBER and CDER Pharmacology/Toxicology reviewers that provided the latest internationally harmonized consensus standards for the proper interpretation of mouse lymphoma gene mutation assay (MLA) data that are submitted as a part of pre-clinical safety evaluations. Reviewers submitted troublesome data sets, and the interpretation of positive and negative responses was discussed. The information in the training class was the result of a multiple-year effort by the Mouse Lymphoma Assay Workgroup of the International Workshop on Genotoxicity Test Procedures (IWGT) to standardize the MLA. The MLA workgroup is comprised of experts from Japan, Europe, and the United States and is chaired by NCTR.

In FY 2007, analytical methods were developed so the FDA could detect and quantify levels of melamine and cyanuric acid in pet and human food samples. However, the standards needed to validate the methods were not commercially available. NCTR synthesized and supplied melamine and cyanuric acid standards that were vital for the development and validation of the methods in a number of laboratories across U.S. federal agencies. In collaboration with CVM, NCTR has initiated a protocol to study the potential toxic effect on the kidney from a combined exposure to melamine and cyanuric acid.

Five Year Funding Table with FTE Totals

Fiscal Year	Program Level	Budget Authority	Program Level FTE
2005 Actual	$40,206,000	$40,206,000	187
2006 Actual	$40,739,000	$40,739,000	190
2007 Actual	$42,056,000	$42,056,000	183
2008 Enacted	$44,006,000	$44,006,000	190
2009 Estimate	$45,816,000	$45,816,000	190

Budget Request

The FY 2009 President's Budget requests $45,816,000 in program level funding for the NCTR, including the support of 190 FTE. The request represents an increase of **$**1,810,000 over the FY 2008 enacted level. The overall increase provides additional budget authority to cover a targeted increase for the food protection initiative, and cost of living pay increase for the modernizing medical product safety and development initiative.

Protect America's Food Supply Initiative

The FY 2009 President's Budget request for the Protecting America's Food Supply Initiative is $6,056,000, an increase of $1,733,000 over the FY 2008 enacted level. Base funding for the NCTR supports research in its program areas. The goal of these program areas is to enable FDA to make sound science-based regulatory decisions and improve the health of the American people. Base funding will allow the development of new methods for establishing gender-related biomarkers used by FDA scientists to evaluate efficacy and toxicity of individualized treatments for disease that are not gender-specific. Base funding will enable NCTR to create new methods and techniques used for preventing and detecting both accidental and intentional food contamination.

The FY 2009 budget requests an increase of $1,733,000 for the Protecting America's Food Supply Initiative. Of this amount, $1,683,000 is the NCTR portion of the initiative that will fund development of techniques to detect genes in bacteria that are resistant to multiple antibiotics using microarray technology. In addition, $50,000 is the amount for the cost of living pay increase. The cost of living pay increase will allow NCTR to support its workforce dedicated to achieving the food protection initiative.

The Protect America's Food Supply initiative will allow FDA to accomplish its mission of ensuring the safety of domestic and imported food by implementing priority components of the Food Protection Plan, The initiative will provide a risk-based, production-to-consumption strategy for food and feed safety and defense. The funds for this initiative will allow NCTR to support the development of techniques to detect genes in bacteria that are resistant to multiple antibiotics using microarray technology. Research to determine the genetic diversity of

antibiotic-resistant bacteria will aid in the FDA's evaluation of their intrinsic resistance to multiple antibiotics. This technology will allow FDA to quickly identify disease outbreaks that pose especially high risks for the American public because they involve antibiotic-resistant strains. Additionally, this antibiotic-resistant research can help industry and regulatory agencies design hazard-analysis and critical control-point protocols to safeguard against pathogen contamination during processing.

Modernizing Medical Product Safety and Development Initiative

The FY 2009 budget requests $40,071 000 for Modernizing Medical Product Safety and Development Initiative, an increase of $388,000 over the FY 2008 Enacted level. This amount represents the cost of living pay increase for the NCTR workforce that supports NCTR's Enhancing Product Safety area. The base funding and cost of living pay increase will enable NCTR to initiate studies used to identify biomarkers of exposure and toxicity resulting from the use of nanomaterials. These materials, such as the heavy metal manganese, are used in a wide spectrum of applications including medical diagnostic and treatment equipment. These studies will focus on the effects of these materials on developing neurological systems. This will enable FDA to gain a better understanding of health and safety issues related to the use of nanomaterials. The nanotechnology research will provide a framework for regulatory guidelines for safe and effective use of nanomaterials in FDA-regulated products.

Administrative Savings and Management Efficiencies

The FY 2009 budget request for NCTR reflects a decrease of $311,000. NCTR will recognize these savings through the IT consolidation effort of IT applications that is occurring across the agency.

NCTR Outputs/Outcomes Table

#	Key Outcomes/Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006 Target	FY 2006 Actual	FY 2007 Target	FY 2007 Actual	FY 2008 Target	FY 2009 Target
Long-Term Objective 1: Increase the number of safe and effective new products available to patients.									
1	Use new "omics" technologies and pattern recognition algorithms to analyze imaging data for early-stage disease diagnosis and to study how an FDA-regulated compound or product interacts with the human body. (263101) (output)	Skin tumor induct-ion	1) Bio-markers of liver toxicity 2) PPAR effects on liver gene expres-sion 3) Age-related changes in gene expres-sion	Novel technol-ogies to assess changes in genes	Hepato-toxicity of Type II diabetes drugs	1) Systems biology in drug review 2) Proof of principle that pattern recog-nition can supple-ment MRS brain scan inter-pretation	1) Urinary biomark ers for kidney failure 2) AZT effects on mito-chondria 3) Proto-type algorith m was successf ully develope d from 30 MRS brain scans	1) "Omics" data in the review process 2) Deter-mine limit-ations of the algor-ithms (e.g. staging disease)	Analyze imaging data by appli-cation of pattern recog-nition algorithms to other tissues and diseases
2	Develop computer-based models and infrastructure to predict the health risk of biologically active products. (263102) (output)	Geno-toxicity of liver and lung carcino-gens	Array-Track imple-mented	Inter-pret DNA study using Array-Track	Micro-array studies on nutri-tional supple-ments com-frey and aristo-lochic acid.	Utility of Array-Track and training for reviewers	1) JMP® and Array-Track ™ integra-tion 2) Regu-latory training on Array-Track™	Bio-infor-matics data package	Expand Array-Track
Long-Term Objective 2: Prevent safety problems by modernizing science-based standards and tools to ensure high-quality manufacturing, processing, and distribution.									
3	Develop risk assessment methods and build biological dose-response models in support of Food Security. (264101) (output)	1) White paper with CFSAN/ CVM on Nutri-tion Re-search 2)Surro-gate mic-robes	*Salmo-nella* biochip	Oligo-nucleo-tide micro-array method	Method to screen 131 anti-biotic resist-ance markers	Flow cytometry tech-nology	1) Test kits and methods for patho-gens 2) Addi-tional *Salmo-nella* biochip	Ricin screen-ing assay	1) Rapid pathogen detection 2) Antibiotic resistance markers

Long-Term Objective 3: Detect safety problems earlier and better target interventions to prevent harm to consumers.									
4	Develop standard biomarkers to establish risk measures for FDA-regulated products. (264201) (output)	Study Ketamine using Micro-PET Imaging – BSL3 lab	1) Neuro-imaging in non-human primates 2) Data from PET technology	Neuro-pathology and behavioral risk as predictor	1) Behavioral effects of acrylamide 2) Concurrent neuro-pathological analysis	Carbon nano-materials methods and ketamine research	1) Ketamine induced neuro-toxicity in primate model 2) Synthesis methods for nano-tubes	Micro-array data standards	Biological effects of manganese nano-particles

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.** (263101)

   Context: With the advent of new technologies such as toxicoinformatics, proteomics, metabolomics, and genomics, and the expansion of existing technologies such as imaging and nanotechnology, the FDA has the necessary tools to detect disease at an earlier stage and to better understand how an FDA-regulated compound or product interacts with the human body. The accelerated rate at which technological advances are being made in the marketplace dictates that the FDA also accelerates its rate of innovation in the regulatory research arena, which is why this NCTR goal is also featured as a goal in the Department of Health and Human Services (DHHS) Strategic Plan. FDA's goal to determine the feasibility of using systems biology in the drug review process and the development of a test case with a collaborative partner is a step toward the development of safer and more effective therapies that replace one-size-fits-all drugs. Treatments that focus on specific population needs will help provide personalized nutrition and medicine to the American public.

   Performance: In FY 2007, NCTR conducted two studies analyzing metabolites in urine samples to identify biomarkers for adverse reactions and susceptibility to toxicity, and also conducted research on the side-effects of anti-HIV drugs. In collaboration with the University of Arkansas for Medical Sciences (UAMS) and the University of Cincinnati, NCTR analyzed samples from children during and after cardiac surgery. This resulted in the detection of a mechanistic biomarker at 4 and 12 hours after cardiac surgery for patients who, two or three days after the surgery, developed acute kidney failure. In a separate study, in collaboration with CDER, NCTR analyzed urine samples to investigate age-related differences in susceptibility to toxicity, especially in the pediatric population. The results from the study with CDER showed that an increase in urinary glucose is a biomarker of liver toxicity and that hydroxyproline (an amino acid) and glucose are biomarkers in antibiotic-induced renal toxicity. Additionally in FY 2007, NCTR studied the effects of anti-HIV drugs (AZT) on mitochondrial function. Drug-induced toxic effects on mitochondria were investigated in the liver and the skeletal muscle of infant mice exposed to AZT just before and after birth. The knowledge gained by using these genomic approaches in research can potentially improve treatment strategies for cardiac and HIV-infected patients, and particularly the pediatric patients.

2. **Develop computer-based models and infrastructure to predict the health risk of biologically active products.** (263102)

Context: To effectively support large datasets generated using new technologies such as toxicoinformatics, proteomics, metabolomics, and genomics, NCTR scientists develop and enhance scientific analytical software in collaboration with colleagues from government, academia, and industry to advance the incorporation of this data analysis into the regulatory process. NCTR's key objective is to develop computer-based models and infrastructure to predict the health risk of biologically active products. ArrayTrack™ is software invented by NCTR scientist that allows for the management, analysis, and interpretation of vast amounts of omics date. The FY 2007 goal to demonstrate the utility of ArrayTrack™ in the regulatory environment, continue training of reviewers, and initiate testing of an additional ArrayTrack™ module is an important step towards the American public benefiting from the vast amount of bioinformatic data being generated from the new technologies. The expanded use of Arraytrack™ and other bioinformatic tools allows the FDA to support the rapid translation of scientific research into reliable and safer treatments by improving the management of available data**.**

Performance: The widely used JMP® Genomics software has been integrated with the FDA genomic tool, ArrayTrack™, under a Cooperative Research and Development Agreement (CRADA) between NCTR and SAS. The newly integrated module allows reviewers and scientists to toggle between the two software platforms to access the analysis functions available from both genomic tools. Additionally, NCTR has continued to provide regulatory training to FDA reviewers on the use of ArrayTrack™. NCTR also has developed several new functions in ArrayTrack™ to support the Voluntary Genomic Data Submission (VGDS) program, the CommonPathway tool and the Significance Analysis of Microarray (SAM) Data method. The CommonPathway allows for integrated analysis of multiple "omics" data in the VGDS review. The SAM Data method enhances the ability to identify genes from differently treated groups, which will allow for more accurate results in the genomic-data review process.

3. **Develop risk assessment methods and build biological dose-response models in support of Food Security.** (264101)

Context: To address research needs and build the capability to assess and reduce food-related health threats, NCTR researchers evaluate key regulatory issues of food safety, conduct multidisciplinary studies to develop risk assessment methods, and develop biological doses-response models vital to food security. NCTR's FY 2007 goals to incorporate flow cytometry technology into regulatory procedures to rapidly identify terror agents and continue development of additional *Salmonella* biochips will help in the development and validation of new technologies for rapid identification of contaminants and intervention strategies to reduce threats to human health.

Performance: In FY 2007, NCTR developed flow cytometry methods and associated kits that could be used as detection tools. Assays for three foodborne pathogens (*Salmonella* spp., *Listeria* spp., and *E. coli* general) also were developed and are now beginning Association of

Official Analytical Chemists validation. The methods are being expanded to detect more hazardous foodborne pathogens like *E. coli O157* and the bacteria that causes botulism, as well as in clinical areas like the detection of tuberculosis and multiple antibiotic-resistant staph. Additionally in FY 2007, NCTR developed a *Salmonella* biochip to characterize multiple antibiotic-resistant *Salmonella* strains. This research and other Food Protection research activities at NCTR will allow the FDA to reduce the spread of foodborne outbreaks and enable the development of intervention strategies to reduce the frequency of multi-drug resistant pathogens in the U.S. food supply.

4. **Develop standards biomarkers to establish risk for FDA-regulated products.** (264201)

Context: NCTR's research to develop tools, methods, and standard biomarkers to manage or assess risk associated with the products regulated by FDA helps prevent potential health-endangering products to remain in and continue to enter the marketplace. NCTR's research increases the number of safe and effective medical products available to the public by integrating new automated tools and standards into the review and evaluation of FDA-regulated products at all stages of the product lifecycle. By increasing the understanding of the biological effects and toxicity of nanomaterials, FDA will be able to identify biomarkers of toxicity thus providing early recognition of potential safety issues before they become adverse events in the general population. In addition, the regulatory guidelines will assist industry in identifying the most promising uses of this technology resulting in more cost effective product development.

Performance: In FY 2007, NCTR conducted research on the behavioral changes associated with long-term exposure to the pediatric anesthetic, ketamine, and other related compounds. Gene changes associated with acute exposure to ketamine during the peak of the brain growth spurt and ketamine-induced neuronal cell death were examined. NCTR is conducting animal studies with ketamine to determine the level of safety during all stages of pregnancy and early childhood; the relationship of dose-level and anesthesia duration to cell death; and the permanency of damage to brain cells. The results from these studies are not only providing fundamental insight into normal developmental processes, but are also providing important data to guide pre- and post-market regulatory decisions and guidance for future preclinical and clinical studies. Also, in FY 2007, NCTR via an outside collaboration developed synthesis methods for carbon nanofibers, multi-wall carbon nanotubes, and double-wall carbon nanotubes. Among the accomplishments resulting from this collaboration is a novel method for preparing high quality delivery devices used in medical products.

NCTR Program Activity Data (PAD)

NCTR WORKLOAD AND OUTPUTS	FY 2007 Actuals	FY 2008 Estimate	FY 2009 Estimate
Research Publications	126	135	185
Scientific Presentations	182	165	180
Patents (Industry)	5	2	2
Leveraged Research			
Federal agencies (Interagency Agreements)	7	3	2
Nongovernmental organizations (CRADAs)	17	16	11
Active Research Projects			
Personalized Nutrition & Medicine	77	84	84
Food Protection	31	32	36
Enhancing Product Safety	63	74	74