NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

The FY 2010 program level budget request for the FDA's National Center for Toxicological Research is $58,745,000.

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

FDA Program Resources Table

	FY 2008		FY 2009 Omnibus	FY 2010 President's Budget Request	FY 2010 +/- FY 2009 Omnibus
	Enacted	Actuals			
Program Level	**$47,402,000**	**$44,443,000**	**$52,511,000**	**$58,745,000**	**$6,234,000**
Center	$47,402,000	$44,443,000	$52,511,000	$58,745,000	$6,234,000
FTE	196	192	198	210	12
Program Level FTE	**196**	**192**	**198**	**210**	**12**
Budget Authority	**$47,402,000**	**$44,443,000**	**$52,511,000**	**$58,745,000**	**$6,234,000**
Center	$47,402,000	$44,443,000	$52,511,000	$58,745,000	$6,234,000
Pay Increase (non add)				*$690,000*	$690,000
Protect America's Food Supply (non-add)				*1,625,000*	1,625,000
Safer Medical Products (non-add)				*$3,919,000*	$3,919,000
Budget Authority FTE	196	192	198	210	12

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

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.

* 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.

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 the mission of protecting public health such as:

- developing scientific processes to advance FDA towards personalized medicine (individualized therapy and disease susceptibility)
- identifying early predictors of risk of toxicity of regulated products
- developing, validating, and providing guidance for the regulatory use of new technologies
- providing regulatory tools that facilitate premarket review, postmarket safety assurance, and risk-based product safety decisions
- evaluating the biological effects of potentially toxic chemicals or microorganisms
- providing key research data for high priority safety issues
- performing research in the areas of food safety and food defense
- facilitating expedited development of regulated products to improve 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 such as drugs, devices, biologics, cosmetics, and nutrients to improve the health of Americans. While the research strategies of the 20th century yielded data and knowledge that extended our average life span and improved personal and public health, much of that knowledge was based on the average response of a population to a food, nutrient, or environmental chemical or the average risk for carrying a specific allele of a gene involved in a disease. Such knowledge may or may not be applicable to an individual with different genotypes or environmental exposures. 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 indicators will aid the FDA in developing science-based individualized treatment therapies that will increase treatment effectiveness and reduce the rate of adverse events in patients. NCTR will explore new approaches such as nutrigenomics to better understand how individual attributes affect responses to drugs, foods, nutrients, and dietary supplements.

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 Initiative*. 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 healthcare 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 2005 through FY 2008, combined with FY 2009 and 2010 goals, indicates NCTR is meeting or exceeding most personalized nutrition and medicine targets. NCTR is developing research strategies that account for genetic, environmental, and cultural diversity that influence expression of genetic make-up and produce knowledge for improving personal and public health. NCTR is also 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 will continue research to define the correlations between an individual's nutrition, health, and genetic profile. These new and innovative projects are conducted with local-community participation. This increased understanding can be used to develop personalized dietary recommendations which may improve the health of individuals and communities.

NCTR accomplishments in FY 2008 support the goal of personalizing nutrition and medicine. A manuscript submitted for publication described the results of a prototype pattern-recognition algorithm that detects normal and anomalous tissue developed from more than 30 non-invasive magnetic resonance spectroscopy (MRS) brain scans. The algorithm was developed to increase the ease and accuracy of interpreting complex MRS scans that are expected to detect early-stage cancers. In 2008, NCTR also expanded the study to include a training set of almost 150 brain scans representing multiple types of tumors and normal scans. Ultimately the goals of these projects are to develop and apply pattern-recognition algorithms to identify early manifestations of brain disease, to classify and grade tumors, and to use the algorithms in other clinical applications such as the detection of breast and prostate cancer markers. These projects are anticipated to lead to improved tumor diagnostic techniques and provide more affordable noninvasive tissue screening for disease.

In 2008, NCTR organized and led the eighth Microarray Quality Control (MAQC) meeting, as part of the second phase of the MAQC project, with participants from across the government, academia, and industry. MAQC I focused on the reproducibility of gene expression experiments and resulted in an FDA companion guidance document for pharmacogenomic data submissions. MAQC II aims to standardize microarray data analysis by building consensus for "best practices" in the development and validation of microarray-based predictive models. It is expected that an FDA guidance document on the appropriate use of microarray genomic data in clinical and preclinical settings will be developed based on findings from the MAQC-II project. More than fifteen manuscripts generated from the MAQC-II project have been submitted for peer-reviewed publication.

NCTR initiated a Community-Based Participatory Research (CBPR) project, in conjunction with the USDA, in the Lower Mississippi Delta as a means to capture and assess individual nutritional, environmental, and activity exposures. The project is being conducted in this area because there is a severe problem with adult obesity and the risk for obesity in children is significantly higher than the national average. The pilot project examined the effect of better nutrition on serum levels of certain vitamins and metabolites in children enrolled in a 2008 obesity prevention summer camp for youth. Data generated can improve the basis of public health policies and inform those interested in developing improved access to food and healthcare in the Delta region.

In addition, NCTR scientists applied their classification algorithms, Classification by Ensembles from Random Partitions (CERP), which integrate data from omics and environmental assessments to identify gender-specific biomarkers for individualized treatment of non gender-specific disease such as liver disease. Ideally, patient treatment should be based on an individual's disease characteristics and risk factors. The identification of gender-specific biomarkers from microarray gene expression data will aid in evidence-based and validated biomedical decision-making.

In 2008, NCTR acquired and installed a high-resolution dedicated positron emission tomography (microPET) instrument in a specialized NCTR Imaging Facility that will be used in preclinical studies on the development of toxicity. This noninvasive imaging tool allows for an increased level of data from animal models and provides a direct link to clinical applications. Biomedical imaging has the potential to play an important role in drug-development processes and the diagnosis of disease in vital organs such as the heart, liver, and brain. Imaging devices that reveal clinical and pharmacogenomic information will individualize medicine both for the diagnosis and treatment of disease, and allow for monitoring the efficacy of treatment regimens.

<u>Food Protection</u>

In support of Food Protection, the public health goals of NCTR are prevention and intervention. NCTR's Food Protection program will develop techniques to *prevent* contamination of the food supply and 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 and the environment. To support this goal, NCTR is expanding its capability to identify, assess, rapidly respond to, 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 seeks to enhance the nation's healthcare 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.

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 2005 through FY 2008, combined with FY 2009 and 2010 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 3) reduce the frequency of multidrug-resistant microorganisms and key pathogens in the U.S. food supply. The research conducted by the NCTR contributes to FDA's goal of increasing food protection for the public.

NCTR will continue research projects to further evaluate metabolomic and bacterial signatures of drink spoilage in milk. This investment should lead to a better understanding of the interactions between bacteria in milk, which may help to reduce or eliminate organisms that lead to spoilage. NCTR will also continue the development of an integrated genomic knowledge base for *Salmonella* including identification of knowledge gaps and development of projects to address those gaps. The goal is to increase identification and understanding of food vulnerabilities.

In 2008, NCTR investigators developed a cell-based assay method and a biochemical assay to detect and measure the activity of ricin and related toxins in diverse foods such as infant formulas, fruit juices, yogurt cultures, and peanut butter. The assay methods are very

sensitive and detect many cytotoxic agents with food-safety relevance, including the Category B select agents of ricin, abrin, Shiga toxin, the mycotoxin fumonisin B_1, and the toxic transition metal ions cadmium, iron, and copper, that are found in diverse types of food. Applied studies performed using this method showed that ricin is not inactivated by the typical pasteurization conditions used in manufacturing infant formulas and fruit juices. Ultimately, the evolving progress on these studies demonstrates the need to leverage resources to develop technology that extracts toxins from contaminated produce and other solid surfaces.

To support the Food Protection Plan, NCTR completed an Interagency Agreement with USDA and Homeland Security to determine the survivability of *Bacillus anthracis* in processed liquid-egg products which includes whole eggs, egg yolks, and egg whites stored at permissive and non-permissive temperatures. The requirements for survival and inactivation of a surrogate strain of *Bacillus anthracis* (Sterne strain) in these products were determined. Data from this research will be applied to assessing risks resulting from deliberate inoculation of anthrax spores in a high-value food matrix.

In 2008, NCTR scientists applied the NCTR-developed genomic tool, Mitochip, to a mouse model to determine the mechanism by which a weight-loss dietary supplement and natural metabolic stimulant, usnic acid, causes liver toxicity. Usnic acid is an organic compound with antimicrobial properties and has been used as an active ingredient or as a preservative in several consumer products, including creams, toothpastes, mouthwashes, deodorants, shampoos, and sunscreens. Understanding the drug-induced toxic effects on mitochondria in the liver will aid researchers in determining the human risk of exposure to low levels of usnic acid that are present in dietary supplements currently being marketed as antimicrobials.

Recently, NCTR scientists developed a rapid molecular method that can identify multi-drug resistant *Salmonella* from food samples. Recent collaborations with NCTR and the Office of Regulatory Affairs (ORA) on imported seafood *Salmonella* isolates have provided new information on the prevalence of antibiotic-resistant genes. The genetic fingerprinting was helpful in identifying similar strains isolated from different seafood samples, in different countries and years. The Centers for Disease Control (CDC) and Prevention estimate approximately 1.4 million cases of Salmonellosis occur annually in the U.S. causing significant economic loss and substantial morbidity. This study provides an understanding of the frequency and mechanism of antibiotic resistance in imported seafood products and enhances the FDA's mission to increase safety in the food supply domestically and abroad.

In 2008, NCTR determined that human intestinal microflora play a key role in the metabolism of azo dyes used in cosmetics, food products, textiles, plastics, and pharmaceuticals. The metalobolism of azo dyes by the human body is important because some azo dyes are known carcinogens. The study found that the human intestinal microflora are capable of degrading azo dyes found in contaminated foods and toxic aromatic amines, which is a potential danger to the American public. This information allows FDA scientists to gain a clearer understanding of how food contaminants affect the

intestinal microflora and how changes in the microflora may affect human health. It also provides the FDA with new information to consider when assessing the risk of azo dyes in food products.

Enhancing Product Safety

Under Enhancing Product Safety, NCTR scientists conduct customized bioassessments of regulated products. The goals of Enhancing Product Safety are to translate toxicity data into a comprehensive risk-based evaluation and 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 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.

NCTR regulatory research in support of Enhancing Product Safety expanded 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 to establish new scientific tools, especially in the area of bioinformatics. NCTR's overall performance to date for FY 2005 through FY 2008, combined with FY 2009 and FY 2010 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.

In support of the goal to Enhance Product Safety, NCTR is conducting ongoing research on the pediatric anesthetic, ketamine, in collaboration with CDER. Ketamine is in a class of anesthetic compounds that cause neurodegeneration when administered during development in rodents. To determine the clinical relevance of the rodent studies, scientists are evaluating the neurological effects of ketamine use in developing nonhuman primates, an animal model closely related to the human infant. Ketamine-treated animals are being assessed to determine the level of safety during all stages of pregnancy and early childhood development. Obtaining data on the relationship of dose-level and anesthesia duration to cell death and the permanency of damage to brain cells, will provide pivotal information for assessing the potential public-health risk associated with the pediatric use of agents such as ketamine and other anesthetic agents. 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 pre-clinical and clinical studies. NCTR will continue to develop noninvasive techniques using imaging systems to determine if the use of anesthetics in children is associated with memory and learning deficits or other changes in the central nervous system. Development of these techniques will help FDA better understand the risks and benefits of anesthetic use in children that can lead to improved guidelines.

NCTR has made large strides in establishing itself as the core source of nanotechnology knowledge for the FDA. NCTR will support nanotechnology studies with the newly

created NCTR/ORA Nanotechnology Core Facility (NCF) by providing analytical support, materials characterization, and electron microscopy support. Critical equipment purchases have been made and NCTR will be hiring one additional FTE, an electron microscopy technician. By conducting this research, FDA will have a better understanding of the consequences of human exposure to nanoscale materials so that FDA may provide guidelines for the safe and effective use of these materials in regulated products.

In FY 2008, NCTR implemented the Science Training and Exchange Professional (STEP) Development Program to facilitate and strengthen the sharing of scientific expertise, tools and technology across the FDA Centers through short-term training or research. In its first year of the program NCTR accepted 12 scientists from CDRH, CVM, CFSAN, and ORA. This short-term training and exchange program is designed to enhance the professional development of Agency scientists through hands-on training, encourage the exchange of technical information on new laboratory methods and technologies, and foster networking and collaborations.

NCTR also established a secure, digital-imaging and software system to be used in the formal peer review of Good Lab Practices (GLP) studies. This virtual-pathology environment significantly reduces procedural costs and facilitates the organization of global professionals producing the most expert and timely reviews possible. Using advanced digital scanners, computer networks, and sophisticated software, it is possible to make high-resolution, high-quality images of samples and send them anywhere in the world for analysis within hours rather than days. This new digital pathology technology implemented at NCTR and featured in "*Government Health IT*," enables military doctors, government scientists, and university researchers to speed diagnoses and save lives.

NCTR scientists are actively working with the CDER genomic group to review genomic data from Voluntary eXploratory Data Submissions (VXDS) using ArrayTrack™. A manuscript titled "ArrayTrack™ – An FDA and Public Genomic Tool" has been submitted describing the role of ArrayTrack™ in FDA's VXDS program. NCTR will develop a prototype that integrates an agency-wide bioinformatics data warehouse (Janus databases) with analytical tools such as ArrayTrack™ and SNPTrack in FY2010 to manage and analyze omic data voluntarily submitted through the VXDS process by industry. Because Janus is based on the same model typically used for electronic healthcare records and clinical data repositories, this information can be integrated with the VXDS data and analyzed to enable earlier detection of adverse events and to foster personalized nutrition and medicine. An efficient and integrated bioinformatics infrastructure within the agency is essential to review and understand how sponsors reach their biological conclusions and to ensure the incorporation of omics data into regulatory processes. ArrayTrack™ provides this infrastructure so that the data analysis and interpretation process is simplified and enhanced, enabling FDA to realize the public health benefits of genomic data.

In 2008, NCTR scientists developed Mold2, a software package freely available to the scientific community that rapidly calculates a large and diverse set of molecular descriptors encoded with two-dimensional chemical structure information. Comparative analysis of Mold2 descriptors with those calculated from commercial software on several published

datasets demonstrated that Mold2 produced more predictive models. Predictive modeling can reduce the likelihood that companies will develop a drug compound that fails in animal toxicology studies late in the product-development phase after a large investment of FDA and pharmaceutical resources has been spent. This important decision-support tool allows for improved predictive toxicology that can lead to significant savings of time and money for both the pharmaceutical industry and the FDA, limited testing on animals, and increased safety and effectiveness of new products available to the American public.

Five Year Funding Table

The following table shows a five-year funding history for the National Center for Toxicological Research's program level and budget authority resources.

Fiscal Year	Program Level	Budget Authority	FTE
FY 2006 Actual	$40,739,000	$40,739,000	190
FY 2007 Actual	$42,056,000	$42,056,000	183
FY 2008 Actual	$44,443,000	$44,443,000	192
FY 2009 Omnibus	$52,511,000	$52,511,000	198
FY 2010 Estimate	$58,745,000	$58,745,000	210

Budget Request

The FY 2010 President's Budget request for NCTR is $58,745,000. It is an increase of $6,234,000 above the FY 2009 FDA appropriation level in the Omnibus Appropriations Act, 2009. Base funding for the NCTR supports research in each of NCTR's three program areas of Personalized Nutrition and Medicine, Food Protection, and Enhancing Product Safety. 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.

In the Personalized Nutrition and Medicine program area, new methods for establishing gender-related biomarkers critical to evaluating efficacy and toxicity of individualized treatments for diseases that are not gender-specific will be developed. The ultimate goal of this biomarker research is the development of a user-friendly classification software tool available to the research community. Community-based participatory research is another important area in this program that focuses on identifying the correlation between an individual's nutrition, genetic profile, health, and susceptibility to chronic disease. The increased understanding of gender-specific biomarkers and gene-environment interaction will aid in the proper treatment and management of disease and advance the development of effective and safe medications, dosing regimens, and dietary guidelines that are tailored to an individual's genetic make-up.

In the Food Protection program area, techniques are developed to help prevent and detect both accidental and intentional food contamination. A primary goal of Food Protection research is to develop faster and easy-to-administer methods for earlier detection of microbial or chemical contaminants in the American food supply. This initiative will allow FDA to increase its prevention and remedy of food contamination by arming reviewers and industry with an arsenal of faster microbial detection methods and techniques.

In the Enhancing Product Safety program area, studies will be initiated to identify biomarkers of exposure and toxicity resulting from the use of nanomaterials such as the heavy metal manganese 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 the safe and effective use of nanomaterials in FDA-regulated foods, cosmetics, and medical products. NCTR will continue to conduct studies to understand the toxicological and biological impact of animal 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. Improved understanding of nanomaterials, their transport, and their toxicity will provide a framework for regulatory guidelines for safe and effective use of nanomaterials to provide early recognition of potential safety issues before they become adverse events. FDA has already reviewed and approved some nanotechnology-based products, and expects a significant increase in the number of nanoscale materials in drugs, devices, biologics, cosmetics, and food.

National Center for Toxicological Research (NCTR) Performance Measures Table

Long Term Objective: Provide consumers with clear and timely information to protect them from foodborne illness and promote better nutrition.

Measure	FY	Target	Result
262401: Develop biomarkers to assist in identifying the correlation between an individual's nutrition, genetic profile, health, and susceptibility to chronic disease in support of personalized nutrition and health. *(Output)*	*2010*	Interpret data collected in the Delta Vitamin Obesity Study	December 2010
	2009	N/A	N/A
	2008	N/A	N/A

Long Term Objective: Increase the number of safe and effective new medical products available to patients.

Measure	FY	Target	Result
263101: 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. *(Output)*	*2010*	1) Demonstratable tool to use in the drug-review process based upon the liver toxicity knowledge base 2) Develop translatable biomarkers for studying pediatric products (e.g. ketamine, methylphenidate)	December 2010
	2009	Analyze imaging data by application of pattern-recognition algorithms to other tissues and diseases	December 2009
	2008	1) Omics data in the review process 2) Determine limitations of the algorithms (e.g. staging disease)	1) 7 VXDS submissions reviewed using omics tools (Target Met) 2) Algorithm able to classify four disease categories (Target Met)
	2007	1) Systems biology in drug review 2) Proof-of-principle that pattern recognition can supplement MRS brain scan interpretation	1) Urinary biomarkers for kidney failure (Target Met) 2) AZT effects on mitochondria (Target Met) 3) Prototype algorithm was successfully developed from 30 MRS brain scans (Target Met)
	2006	N/A	Hepatotoxicity of Type 2 diabetes drugs (Target Met)

Measure	FY	Target	Result
	2005	N/A	1) Biomarkers of liver toxicity (Target Met) 2) PPAR effects on liver-gene expression (Target Met) 3) Age-related changes in gene expression (Target Met)
263102: Develop computer-based models and infrastructure to predict the health risk of biologically active products. *(Output)*	*2010*	Add metabolomics module to ArrayTrack™	December 2010
	2009	Expand ArrayTrack™	December 2009
	2008	Bioinformatics data package	SNPTrack Version 1 developed (Target Met)
	2007	Utility of Array Track™ and training for reviewers	1) JMP® and ArrayTrack™ integration (Target Met) 2) Regulatory training on ArrayTrack™ (Target Met)
	2006	Interpret DNA study using ArrayTrack™	Microarray studies on nutritional supplements, comfrey and aristolochic acid. (Target Met)
	2005	Develop a computer-based system to integrate databases, libraries and analytical tools	ArrayTrack™ implemented (Target Met)

Long Term Objective: Improve the medical product review process to increase the predictability and transparency of decisions using the best available science.

Measure	FY	Target	Result
263201: Develop science base for supporting FDA regulatory review of new and emerging technologies. *(Output)*	*2010*	Validate SOPs for detection of nanoscale materials in FDA-regulated products in collaboration with ORA/ARL	December 2010
	2009	Operational joint NCTR/ORA Nanotechnology Core Facility	December 2009

Long Term Objective: Prevent safety problems by modernizing science-based standards and tools to ensure high-quality manufacturing, processing, and distribution.

Measure	FY	Target	Result
264101: Develop risk assessment methods and build biological dose-response models in support of Food Protection. *(Output)*	*2010*	1) Rapid detection toolkits for foodborne pathogens applicable to fresh produce; evaluate in field situations 2) Begin research on Bisphenol A (BPA), a component in baby bottles and formula containers	December 2010

Measure	FY	Target	Result
	2009	1) Rapid pathogen detection 2) Antibiotic resistance markers	December 2009
	2008	Ricin screening assay	Cell-based assay and PCR-based biochemical assay developed (Target Met)
	2007	Flow cytometry technology	1) Test kits and methods for pathogens (Target Met) 2) Additional *Salmonella* biochip (Target Met)
	2006	N/A	Method to screen 131 antibiotic resistance markers (Target Met)
	2005	N/A	*Salmonella* biochip (Target Met)

Long Term Objective: Detect safety problems earlier and better target interventions to prevent harm to consumers.

Measure	FY	Target	Result
264201: Develop standard biomarkers to establish risk measures for FDA-regulated products. (Output)	2010	1) MAQC—draft guidance document for microarray standards 2) Identify gender-specific biomarkers that enable improved risk/benefit decisions for treatments	December 2010
	2009	Biological effects of manganese nanoparticles	December 2009
	2008	Microarray data standards	MAQC-II results are in and 15 manuscripts on track for March 2009 submission (Target Met)
	2007	Carbon nanomaterials methods and ketamine research	1) Ketamine-induced neurotoxicity in primate model (Target Met) 2) Synthesis methods for nanotubes (Target Met)
	2006	N/A	1) Behavioral effects of acrylamide (Target Met) 2) Concurrent neuropathological analysis (Target Met)
	2005	N/A	1) Neuro-imaging in nonhuman primates (Target Met) 2) Data from PET technology (Target Met)

1. Develop biomarkers to assist in identifying the correlation between an individual's nutrition, genetic profile, health, and susceptibility to chronic disease in support of personalized nutrition and health. (262401)

Context: NCTR's goal is to define the correlations between an individual's nutrition, health, and genetic profile. This research will provide baseline data that supports the FDA goal of providing consumers clear and timely information to help promote personalized nutrition and health. Identifying biomarkers of health, susceptibility to chronic disease, and gene-micronutrient interactions is essential to gaining a more complete scientific understanding of health. NCTR is implementing a novel research program for personalized nutrition and health that relies on the "challenge homeostasis" concept for identifying markers of health and susceptibility. This approach implements a safe, but acute, challenge to the body's ability to regulate and maintain balance. NCTR will use its current omics capabilities, in conjunction with its expanded genomic analyses capabilities, to conduct this research. The intervention design proposed by NCTR establishes a model that may be used by the emerging International Micronutrient Genomics Project that will compare gene-micronutrient interactions across populations and cultures.

Performance: The NCTR Division of Personalized Nutrition and Medicine (DPNM) developed a community-based participatory research strategy for personalizing healthcare. The approach is to analyze genetic and nutrition interactions involved in the predisposition, development, and severity of obesity. The Delta Vitamin pilot study was conducted in 2008 at the Boys, Girls, and Adults Community Development Center Summer Camp in collaboration with the USDA–Agricultural Research Service Delta Obesity Prevention Research Unit. This study introduced the concept of biomedical research to the local community. The research compared the participating children's serum vitamin levels before and after a five week improved diet of healthier foods. The proposed research program for the 2009 Delta Vitamin Study expands the study to include genetic and metabolomic analyses of the local community participants. The FY 2010 goal is to begin to define the correlations between an individual's diet and genetic profile to develop personalized dietary recommendations which may improve the health of individuals and communities.

2. 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)

Context: With the advent of new technologies such as toxicoinformatics, proteomics, metabolomics, and genomics, and the expanding capabilities of noninvasive imaging technologies, 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 FDA accelerate its rate of innovation in the regulatory-research arena. Combining genomic knowledge with microPET imaging is expected to facilitate the search for genetic predictors of drug response. Devices such as microPET that reveal clinical and

pharmacogenomic information will serve to individualize medicine both for the diagnosis and treatment of disease, and allow for monitoring the efficacy of treatment regimens.

Performance: In FY 2008, NCTR scientists expanded a pattern-recognition algorithm that was developed to increase the ease and accuracy of interpreting complex magnetic resonance spectroscopy (MRS) scans from more than 30 brain scans to include a set of almost 150 brain scans. In FY 2009, the goal is to develop and apply pattern-recognition algorithms to identify early biomarkers of brain disease and to use algorithms to analyze imaging data of other tissues and diseases such as breast and prostate cancer. NCTR's FY 2010 goal in this area, to develop translatable biomarkers for studying pediatric products, is especially critical as advances in pediatric and obstetric surgery have resulted in an increase in complexity, duration, and number of anesthetic procedures. To minimize risks to children resulting from the use of anesthesia, it is necessary to understand the effects of anesthetic drugs on the developing nervous system by determining the time-course of neuronal-cell death induced by ketamine administered repeatedly in living animals. NCTR will conduct studies using noninvasive microPET imaging to determine clinical relevance to the pediatric population.

3. 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 scientists that allows for the management, analysis, and interpretation of vast amounts of omics data, and is an important tool for the American public to benefit from the vast amount of bioinformatic data being generated from the new technologies. The expanded use of ArrayTrack™ and other bioinformatic tools allows FDA to support the rapid translation of scientific research into reliable and safer treatments, and better risk evaluations by improving the analysis and management of available data**.**

Performance: In FY 2008, NCTR developed a bioinformatics infrastructure, SNPTrack Version 1, for genotyping-data management, analysis, and interpretation which has been used in VXDS reviews. The FY 2009 and FY 2010 goals to expand ArrayTrack™ to accommodate the analysis of other omics data such as proteomics and metabolomics will even further simplify and enhance FDA's data analysis and review process. Another important accomplishment in FY 2008 is the selection of ArrayTrack™ by Eli Lilly for their clinical gene-expression data storage and baseline analysis. ArrayTrack™ was chosen as Eli Lilly's data management and analysis tool because of its architectural structure, quality, security, and its ability to support their gene-expression studies.

4. Develop science base for supporting FDA regulatory review of new and emerging technologies. (263201)

Context: NCTR's goal to develop a science base to support the FDA regulatory review of new and emerging technologies by establishing a joint NCTR/ORA Nanotechnology Core Facility will strengthen the FDA's ability to prevent potential health-endangering products from entering the marketplace. It is anticipated that NCTR's nanotechnology research program will expand as the number of nanoscale products the regulated community seeks to market increases. The FDA has already reviewed and approved some nanotechnology-based products, and expects a significant increase in the use of nanoscale materials in drugs, devices, biologics, cosmetics, and food. 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.

Performance: In FY 2008, NCTR identified collaborations, funding, and resource requirements to facilitate the establishment of the NCTR/ORA Nanotechnology Core Facility. NCTR is currently conducting studies in FY 2009, which will extend into FY 2010, to understand the toxicological and biological impact of animal 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. Research plans in this area for FY 2010 include studies to quantify the migration of nanosilver from food-contact materials, and determine the conditions under which migration will occur.

5. Develop risk assessment methods and build biological dose-response models in support of Food Protection. (264101)

Context: To address research needs and build the FDA's 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 dose-response models vital to food security. Identifying the prevalence of antibiotic-resistant genes and the genetic fingerprinting of these genes will help identify similar strains isolated from different samples. Another food-related health threat, especially for infants and children, is the presence of Bisphenol A (BPA), an endocrine disruptor that can mimic hormones and a compound used in a wide variety of household items including baby bottles, drinking bottles, and liners for canned food. NCTR will be initiating studies in collaboration with the NIEHS National Toxicology Program to address the health concerns associated with exposures to low doses of BPA during critical periods of perinatal development. Effects reported include alterations in central nervous system (CNS) anatomy, lesions in prostate and mammary glands, urinary tract abnormalities, and the early onset of puberty.

Performance: NCTR will support the implementation of the Food Protection Plan by hiring five researchers and providing equipment to develop test systems for neurotoxins

(including Class B select agents) and develop tests to rapidly identify and characterize strains of the foodborne microbial pathogen *Salmonella*. NCTR's development of a ricin-screening assay and a PCR-based biochemical assay in FY 2008 resulted in three manuscripts being submitted for publication and five presentations given at national meetings, including the annual Society of Toxicology meeting in March 2008. Both assay systems developed at NCTR will be applied in FY 2009 to validate new technologies for rapid identification of contaminants and intervention strategies to reduce threats to human health. In FY 2010 NCTR will work toward the development of rapid- detection toolkits for foodborne pathogens. The goal is for these toolkits to be applicable to fresh produce and also be usable in the field. These goals and the goal to identify antibiotic-resistant markers 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.

6. Develop standard biomarkers to establish risk measures for FDA-regulated products. (264201)

Context: NCTR's research to develop standard biomarkers to establish risk measures for FDA-regulated products prevent potential health-endangering products from remaining in and continuing 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. FDA's ability to identify gender-specific biomarkers will provide improved risk/benefit decisions for treatments. The resulting treatments that focus on specific population needs will help provide personalized nutrition and medicine to the American public. 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 for nanomaterials will assist industry in identifying the most promising uses of this technology resulting in more cost-effective product development.

Performance: In FY 2008, NCTR organized and led the eighth Microarray Quality Control (MAQC) meeting as part of the second phase of the MAQC project, which is focused on the reproducibility of gene expression experiments and the standardization of microarray data analysis. A document outlining "best practices" in the development and validation of microarray-based predictive models, published in 2008, will provide the research and regulatory communities with a foundation to confidently use microarrays in clinical practice and regulatory decision-making. The goal of this project is to ensure that accurate and reliable predictions can be made based on an individual's microarray profile and that companies will bring more effective diagnostic tools to market. It will also help in the FDA review process as more array-based data is included with industry's voluntary exploratory data submissions (VXDS). The FY 2009 goal to study the biological effects of manganese nanoparticles will help FDA to understand the toxicological consequences of exposure to nanomaterials. The FY 2010 goal in this area, to identify gender-specific biomarkers that enable improved risk/benefit decisions for treatments, is expected to substantially reduce error rates when compared to using standard biomarkers which apply to both sexes.

NCTR Program Activity Data (PAD)

NCTR WORKLOAD AND OUTPUTS	FY 2008 Actuals	FY 2009 Estimate	FY 2010 Estimate
Research Publications	125	155	155
Scientific Presentations	165	180	180
Patents (Industry)	5	6	6
Leveraged Research			
Federal agencies (Interagency Agreements)	6	9	9
Nongovernmental organizations (CRADAs)	21	22	22
Active Research Projects			
Personalized Nutrition & Medicine	59	78	62
Food Protection	51	54	52
Enhancing Product Safety	64	57	47