Food and Drug Administration
FY 2012 Congressional Budget Request
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NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

The following table displays funding and full time equivalent (FTE) staffing levels for FY 2010 through FY 2012.

FDA Program Resources Table

(Dollars in Thousands)

	FY 2010 Enacted	FY 2010 Actuals	FY 2011 Cont.Res	FY 2012 Request	+/- FY 2010 Enacted
Program Level	**$58,745**	**$58,531**	**$58,745**	**$60,294**	**$1,549**
Center	$58,745	$58,531	$58,745	$60,294	$1,549
FTE	210	246	246	215	5
Program Level FTE	**210**	**246**	**246**	**215**	**5**
Budget Authority	**$58,745**	**$58,531**	**$58,745**	**$60,294**	**$1,549**
Center	$58,745	$58,531	$58,745	$60,294	$1,549
Pay Increase (non add)				*$134*	*$134*
Transforming Food Safety and Nutrition (non-add)				*$414*	*$414*
FDA Regulatory Science and Facilities (non-add)				*$1,700*	*$1,700*
Administrative and Contract Savings (non-add)				*-$699*	*-$699*
Budget Authority FTE	**210**	**246**	**246**	**215**	**5**

FDA's National Center for Toxicological Research (NCTR) 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 [1]
Food and Drug Administration Amendments Act of 2007 [1]

Allocation Method: Direct Federal/Intramural

Program Description and Accomplishments

Science is the foundation of FDA's regulatory decision-making process and is vital to protecting and promoting the health of American consumers. Within FDA, NCTR interdisciplinary scientific experts conduct peer-reviewed research to identify health and safety issues related to new medical products, such as nanomaterials, and to evaluate new safety concerns identified with established products. NCTR also conducts research on the risks and benefits of products – and thereby advances the FDA mission of protecting patients and consumers – across the full spectrum of products that FDA regulates. The research at NCTR supports FDA's strategic priorities to:

[1] 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.

- improve global public health through international collaboration including research and information sharing
- provide the public with the accurate, science-based information they need to use medicines and foods to improve their health
- understand how the human body reacts to exposure to toxic agents
- incorporate new technologies to improve the assessment of human exposure, susceptibility, and risk to potential adverse events
- increase the understanding of the interaction between genetics, metabolism, and nutrition.

In addition to conducting research in support of the FDA mission, NCTR provides expert technical advice and training to colleagues. This training enhances FDA's basis for sound science-based regulatory decisions that improve the health of the American people and it supports FDA's strategic priority to develop a world-class workforce.

NCTR receives federal appropriations to execute its mission under the legal authorities listed above. NCTR, established in 1971 as a national scientific resource, conducts research that translates knowledge and technology into processes that improve the ability of FDA and others to assess the safety of FDA-regulated products.

The public health benefits of NCTR's work for the American public include:

- early predictors of toxicity-risk from products that FDA regulates
- development and validation of, and guidance for, new technologies used to regulate foods and medical products
- regulatory tools that facilitate premarket review, postmarket safety assurance, and risk-based product safety decisions
- personalized nutrition and medicine including individualized therapy, dietary recommendations, and identification of disease susceptibility
- evaluation of the biological effects of potentially toxic chemicals and microorganisms
- key research data for high-priority safety issues, such as pediatric anesthetics
- analytical tools to rapidly detect food contamination
- methods that facilitate FDA-regulated product development 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
- promote the international standardization and global harmonization of regulatory science.

NCTR executes its research responsibilities in three subprogram areas:

- Personalized Nutrition and Medicine
- Strengthen Surveillance and Risk Analysis
- Enhancing Medical Product Safety

Personalized Nutrition and Medicine

Base Amount: $24,249,936 (All BA)

Public Health Focus

NCTR conducts regulatory research to support Personalized Nutrition and Medicine by developing strategies and methods and providing resources for improving individual and public health. The overall goal of this research is to develop and implement research strategies that identify genetic, environmental, and cultural diversity factors that affect the course of health and disease. In collaboration with industry, academia, and other government agencies, NCTR works to define and characterize individual responses to FDA-regulated products, thus improving personal and public health.

Public Health Outcome

During the 20th century, data generated by the human genome project laid the foundation for one of the most significant scientific contributions to humankind – an understanding that while humans are genetically similar, each retains a unique genetic identity that contributes to the wide array of observable physical or biochemical characteristics. Much of the knowledge generated in biomedical research over the past century was based on the *average* response of a population to a food, drug, nutrient, or environmental chemical. NCTR research will lead to the identification of an *individual's* response.

Through development of a broad range of studies to characterize biomarkers – or indicators – of health, disease risk, and disease status, NCTR's research promotes Personalized Nutrition and Medicine and HHS priorities to Improve Patient Safety, Reduce Obesity, and Accelerate Scientific Advances in Quality Health Outcomes. These biomarkers will allow FDA to identify science-based individualized treatment therapies that will increase treatment effectiveness and reduce the rate of adverse events in patients. NCTR will continue to explore new approaches such as nutrigenomics – the study of relationships between nutrition and genetics – to better understand how individual attributes affect responses to drugs, foods, nutrients, and dietary supplements used individually and in combination.

Promoting Efficiency

Advances in personalized medicine supported by this subprogram have the potential to revolutionize health care. These advances can identify patients most likely to benefit from or experience adverse reactions from particular drugs. Through more personalized treatments, the American public, the American health care system, and businesses and governments that pay health care costs will save time and money. All parties will escape the cost and failed expectations associated with medical products and therapies that are not safe or effective for individual patients.

Similarly, the interactions between foods, nutrients, and dietary supplements with an individual's genetic make-up can be characterized and used to address safety concerns and health issues, including obesity and the diseases exacerbated by or linked to obesity. Decreasing the incidence of obesity will have long-term beneficial consequences for Americans and the health care system. Obesity and the associated chronic conditions cost the U.S. health care system up to $147 billion a year. A small decline in obesity rates can produce significant savings for the health care system and for the American public.

Obesity Research – Obesity is a major public-health concern because of its relationship to metabolic disorders such as Type 2 diabetes and cardiovascular diseases. A clearer understanding of fat-tissue biology and the development of obesity are critical to identifying potential disease markers or drug targets leading to better treatment of obesity. NCTR is conducting research to identify what genetically predisposes individuals to obesity and the consequent development of metabolic syndrome disease such as diabetes and heart disease. Identifying the genes and dietary components that affect the differentiation of stem cells provides data essential to develop diagnostics and strategies for preventing or delaying the onset of nutrition-related chronic diseases. The data from this research will contribute to FDA's and industry's knowledge for designing healthier manufactured foods.

Obesity and Diabetes Research – NCTR conducts studies with the international and local communities to define the correlations between an individual's nutrition, health, and genetic profile. Scientists are working to define the relationship between obesity and the functions of micronutrients and microbiota in the gastrointestinal tract. To better understand a person's predisposition to obesity, research will be conducted using animal models to characterize how stem cells transform into fat cells. In addition, NCTR is pursuing how exposure to sex hormone-like compounds – found throughout the environment and occurring in natural and processed foods, food and drink containers, and medical devices – affects the body's ability to maintain a stable weight, changes food preferences and responses to stress, and increases an individual's vulnerability to obesity. This research will enrich FDA's and the medical community's knowledge about

the cause of obesity and will provide new information for public-health education and policy decisions.

NCTR works with international collaborations to improve global health. In January 2010, NCTR co-organized with the European Nutrigenomics Organization, a planning workshop to outline principles for creation and implementation of a publicly available Nutrition Phenotype Database. The database will capture, store, analyze, and retrieve data from emerging nutrition research in traditional food composition, frequency questionnaires, biomarkers, and the omics sciences. Omics sciences are fields of study in biology ending in "-omics" such as:

- genomics — study of all genes of a cell or tissue
- transcriptomics — study of messenger RNA molecules which can vary with external environment conditions
- proteomics — study of proteins
- metabolomics — study of chemical processes involving metabolites.

Individual genetic variations are being linked to biological responses, including how drugs are metabolized differently among individuals. Such knowledge will allow medical treatments to be optimized for each individual. Since food components/dietary agents can interact with or regulate a variety of molecular targets involved in metabolism and disease risk, nutrients may also alter the effects of drugs and disease susceptibilities among individuals. The Nutrition Phenotype Database will be a global gateway platform for scientists to integrate and analyze data gathered from nutrition studies conducted around the world, increasing the power of scientists to evaluate the role of nutrition in health and disease.

With its international partners, NCTR will also develop a program called the International Type 2 Diabetes Network to recruit and analyze individuals with newly diagnosed Type 2 diabetes to evaluate and record how genes in individuals with Type 2 diabetes differ among the world's populations. This information will be captured in a database of DNA variations in genes predicted to define drug responsiveness and efficacy and develop a greater understanding of gene-nutrient interactions. While this project involves international collaborations of more than ten countries and benefits the international community, the United States population is one of the most diverse in the world, and the information generated will also be directly applicable to Americans.

Since 2008, FDA/NCTR and USDA/Agricultural Research Service have had an ongoing partnership with a community development center in the Mississippi Delta region of Arkansas to conduct community-based participatory research (CBPR) that studies the effects of dietary intake and its influence on the development of obesity-associated diseases. This ongoing collaboration analyzes dietary intake patterns, micronutrient levels in the blood samples of children and adults, and calories expended. In 2010, scientists from NCTR

analyzed data from a 2009 CBPR study using standard statistical approaches and novel methods to assess individual responses. The study was replicated in 2010, with both interventions involving improved nutrient intakes. The goal was to assess the effects of dietary intake and its influence on the development of obesity-associated diseases such as Type 2 diabetes. Preliminary results showed sex-specific differences in children's response to dietary interventions. The standard statistical approaches found that individuals in Town A (pop. > 1000, 1 food store with fresh vegetables, ~20 miles from a supermarket) had significantly better nutrient intake and serum vitamin levels compared to individuals in Town B (pop. < 1000 people, no fresh markets, and ~30 miles from a supermarket). If the 2010 study data is confirmed, these results have implications for the development of recommendations for nutrient intakes targeted to individuals in differently resourced communities.

In FY 2011 and beyond, NCTR will expand the CBPR project by including school and community-based programs across Arkansas, other locations in the U.S., and international sites. The expanded CBPR will include the association of an individual's response to improved nutrient intakes with their genetic makeup and the likelihood of developing obesity and Type 2 diabetes. By the end of FY 2011, NCTR plans to analyze the DNA sequence of 400 candidate genes from the CBPR participants involved in the obesity and Type 2 diabetes study.

Obesity and Stem Cell Research – Researchers from the NCTR Stem Cell Laboratory presented their initial findings on micronutrients and the effects of different types of fat on stem-cell development at an international nutrigenomics meeting in New Zealand in February 2010. NCTR and the Arkansas Biosciences Institute also hosted a workshop in April 2010, to provide an opportunity for scientists to network and establish new collaborations for stem-cell research. NCTR's continuing research in this area will provide FDA and the medical community insight into the relationship between nutrition and adult obesity. NCTR's main objective is to identify gene expression changes in stem cells that predispose individuals to obesity and the development of obesity-related metabolic disorders such as Type 2 diabetes.

MicroArray and Sequencing Technologies Quality Control – NCTR initially organized the MicroArray Quality Control (MAQC) project with participants from across government, academia, and industry to focus on the reproducibility of gene expression experiments. Their efforts resulted in an FDA companion guidance document for pharmacogenomics — the study of genetic variation's effects on individual responses to drugs — data submissions.

In FY 2010, the second phase of the MicroArray Quality Control (MAQC-II) project was completed under the leadership of NCTR scientists. The MAQC-II results are expected to substantially impact the clinical and regulatory use of genomic data. It is anticipated that findings from MAQC-II will lead to an FDA guidance document to aid industry in developing and validating models for

genetic research. NCTR is currently engaging the scientific community -- including FDA's other Centers and the National Institutes of Health -- to develop guidelines to ensure the reproducibility of genomic research.

The third-phase of the FDA-led MAQC effort, also known as the Sequencing Quality Control (SEQC) project, has reached its first milestone in FY 2010. The project established a baseline reference, which can be used to standardize and streamline research in RNA sequencing. A manuscript describing this finding is being developed. SEQC will help prepare FDA for the next wave of genomic data submissions generated from next-generation sequencing technologies to ensure the safety and efficacy of FDA-regulated products.

A pilot study is being conducted at NCTR and CDER to support the feasibility of a fourth phase of this effort, MAQC-IV. The goal is to develop models based on the patient's genetic make-up to predict how effective a regulated drug will be or if serious adverse drug reactions can be anticipated. These prediction models may be implemented in an online knowledge base to alert reviewers, physicians, and patients of the potential for a drug to cause a serious adverse drug reaction in individuals carrying particular genetic variants *before* the drug is prescribed to or taken by the patient. These research studies should greatly enhance FDA's capability to detect, understand, predict, and prevent adverse drug reactions.

Genomics – In 2009, researchers at NCTR established a Genomics Laboratory for analyzing and re-sequencing genes and have analyzed 46 human and eight primate DNA structures. Individual genetic variations are being linked to biological responses, including how drugs are metabolized differently among individuals. Establishing expertise in the area of genomics is essential for FDA's regulatory mission to enable evaluation of new products and services that are developed on the basis of genomic information. Genomic experiments conducted at NCTR confirm that the full spectrum of adverse genetic mutations induced by chemical agents is detected by the Mouse Lymphoma Gene-Mutation Assay (MLA) – an approved scientific test method used by researchers to detect gene mutation and chromosomal damage. This genomics research has provided definitive proof that the MLA is capable of detecting most, if not all, of the chromosomal mutations known to be involved in human cancer development and other genetically based human disease.

NCTR scientists have also recently completed research that capitalizes on newly developed molecular techniques and techniques to conduct microscopic examination of genetic components of the cell, including chromosomes, genes, and gene products.

NCTR also participated in the Human Variome Project, (http://www.humanvariomeproject.org/), an international consortium of scientists and doctors working to electronically capture and index information on all genetic variations affecting human disease and to link geographically specific databases to international databases. These efforts will generate datasets necessary for

linking individual genetic variation to responses to food, environmental influences, medical treatments, and drugs. This knowledge will allow medical treatments to be optimized for each individual.

Biomarker Development – In order for FDA to continue the important mission of protecting public health, biomarkers — or biological indicators — of health and disease status must continue to be developed. These biomarkers can be directly measured in humans and could improve FDA's ability to evaluate the safety of candidate therapies before using them in humans and to detect drug-induced organ toxicity earlier.

The results of several key studies conducted by NCTR scientists suggest that altered gene expression may be used as biomarkers for cancer risk assessment. NCTR scientists demonstrated in these studies that exposure to chemical carcinogens resulted in altered gene expression. These findings are particularly significant because they demonstrate that different carcinogenic agents induce similar genetic alterations — mutations — in the target organ DNA. In addition, these alterations typically appear early and correspond to those frequently found in tumor cells. The recognition that epigenetic – or "gene-silencing" – mechanisms can have a significant role in the development of cancer has challenged the current approach to carcinogenicity testing and indicates the need for a new generation of cancer biomarkers. One remarkable feature of epigenetic abnormalities is their potential reversibility. Thus, rapid identification and regulation of carcinogens before dissemination into society is critical for the prevention of tumor formation.

Biomarkers are also critical for assessment of drug toxicity. NCTR is researching acetaminophen to expand available data. The majority of research data related to postmarket evaluation of acetaminophen usage is limited to acute pediatric overdose. The data generated from the NCTR research will be used to establish second-generation biomarkers of acetaminophen toxicity in future risk-assessment studies of children receiving therapeutic doses of acetaminophen and children receiving acetaminophen overdoses.

In FY 2010, using microarray-filtered analysis validated by real-time Polymerase Chain Reaction, a scientific technique widely used to amplify DNA, NCTR scientists identified 1,640 different sex-expressed genes, 26 of which were molecular transporters. All of the identified genes are potential sex-specific biomarkers and may be important biomarkers for drug toxicity and efficacy. Understanding the modulation of these biomarkers and their effect on risks will greatly improve patient benefits.

NCTR is also conducting research on cardiotoxicity biomarkers which will increase the understanding of cardiac tissue injury during drug exposure. The biomarkers for cardiotoxicity identified in mice will be potentially valuable tools for earlier detection of organ toxicity during preclinical and clinical safety evaluations.

This earlier detection may reduce the rate of severe heart failure and improve therapeutic patient treatment. An understanding of the causes of toxicity will provide the basis for the design of therapeutic interventions to reduce or reverse heart toxicity. On the whole, this information may prove valuable in designing optimal drug regimens or novel interventions to minimize drug-related toxicity to the heart in clinical practice.

Performance Measures

The following table lists the performance measures associated with this subprogram.

Measure	Most Recent Result	FY 2010 Target	FY 2012 Target	FY 2012 +/- FY 2010
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)*	FY 2010: Patterns were identified from analysis of 2009 CBPR data and preliminary analysis of 2010 CBPR data in serum biomarkers that can be used to monitor dietary intervention protocols to reduce obesity (Target Met)	Identify patterns in serum biomarkers to use in monitoring dietary intervention protocols to reduce obesity	1) Develop analytical methods to assess drug-induced heart damage 2) Identify target genes for obesity and the consequent development of metabolic syndrome diseases and heart disease	N/A

Strengthen Surveillance and Risk Analysis

Base Amount: $13,946,063 (All BA)

Public Health Focus

FDA is responsible for ensuring the safety of foods, food ingredients, and bioengineered foods; defending the food system against terrorist attacks; and identifying food-related health hazards. NCTR's Strengthen Surveillance and Risk Analysis subprogram supports these responsibilities and the HHS priority to implement a 21st Century Food Safety System through research that integrates results with the public-health mission of other FDA Centers and the Office of Regulatory Affairs (ORA). Through these collaborative projects, new methods and risk-based techniques continue to be developed to protect the American public from naturally occurring and intentional contamination of the food supply and the environment. NCTR is expanding FDA's capability to identify, assess, rapidly respond to, and reduce food-related health threats.

Public Health Outcomes

NCTR develops methods to assess and manage risks associated with food products that are adulterated, intentionally contaminated, or otherwise found to be detrimental to human health. These methods enable FDA Centers and other agencies to:

- rapidly determine the source of the contaminant
- closely monitor imported foods to identify contamination with traditional and nontraditional biological agents
- more quickly issue health alerts to the public and to state and local public-health agencies during an outbreak associated with consumption of contaminated foods
- improve modeling of risk-assessment data to analyze the safety of imported food.

Through food protection research, NCTR will continue to develop the tools and science necessary to improve understanding of food-security vulnerabilities and the most effective ways to minimize them. NCTR research will lead to:

- rapid, reliable, and cost-effective methods to detect contaminants in food
- new understanding of mechanisms that contribute to a contaminant's toxicity and the relationship to levels of exposure
- new methods to assess mechanisms of antimicrobial resistance in foodborne pathogens, which will help mitigate their spread
- strategies to reduce the occurrence of multi-drug resistant microorganisms and key pathogens in the U.S. food supply.

The research conducted by NCTR contributes to FDA's mission of increasing food protection for the American public.

Promoting Efficiency

The Centers for Disease Control and Prevention (CDC) estimates that approximately 76 million new cases of food-related illness – resulting in 5,000 deaths and 325,000 hospitalizations – occur in the United States each year. Protecting the food supply and preventing significant negative health and economic effects associated with food-related illness is a fundamental part of FDA's mission and a central focus of the Strengthening Surveillance and Risk Analysis subprogram.

NCTR's research in the area of strengthening surveillance and risk analysis will more rapidly identify foodborne pathogens and their sources. Furthermore, the research will more rapidly determine the spread of antibiotic resistance and the increased virulence of foodborne pathogens. The research conducted within this subprogram will also improve our ability to identify the sources of bacterial contamination along the food supply chain and thereby help avoid the health care costs and other economic burdens associated with foodborne illnesses.

Genomic Knowledge Base – NCTR, in collaboration with CFSAN and USDA, continues the development of an integrated genomic knowledge base that incorporates the tools developed for the ArrayTrack™, a DNA microarray data management, mining, analysis, and interpretation software system. A manuscript describing the utility of ArrayTrack™ for characterizing bacterial foodborne pathogens was published in the journal *BMC Bioinformatics*. Additional tools that will be integrated in the knowledge base will allow for a more efficient analysis of genomics and gene expression data to speed up the understanding of how foodborne pathogens contribute to disease.

Taken together, the tools in the integrated knowledge base should help to accelerate our understanding of foodborne pathogens and aid in identifying their sources. The knowledge base can also provide tools for the analysis of genetic information to complement surveillance data collected by government agencies, which will facilitate development of improved food safety regulations in response to evolving threats.

Rapid Detection Tools and Methodologies – NCTR currently has two rapid detection methodologies, RAPID-B and OMNIPrint, undergoing validation and development.

- RAPID-B:
  LITMUS, LLC, licensed and is deploying this NCTR patented method for real-time, on-site surveillance of food for bacterial contamination. Food Emergency Response Network (FERN) level-2 validation of RAPID-B's assay for *E. coli* O157 was performed in 2009 with over 9 food matrices analyzed including salad, cookie dough, salami, spinach, jalapeño peppers, and ground beef. Results of RAPID-B were more accurate than the reference method. RAPID-B prototype assays for *Salmonella* spp., *Listeria* spp. and *Listeria* monocytogenes, *Vibrio* spp., *Campylobacter* spp. have already been developed and plans are being made for their validation. Future development includes assays for additional bacterial pathogens and viruses. The system is rugged and can be transported and operated at the field site.

  In FY 2010, NCTR developed a RAPID-B assay for *Mycobacterium tuberculosis* and its CRADA partner successfully applied it in human sputum as a pilot study. The RAPID-B assay is capable of acquiring and reporting results in less than 15 minutes per sample with a limit of detection of < 10 bacterial cell counts/ml.

- OMNIPrint:
  OMNIPrint is a method which can detect bacterial or chemical contamination in foods or drug ingredients at a concentration of 0.01 to 0.1% by weight in 15 seconds/sample. Real-time characterization is not precise but can be used to recognize variant samples, to indicate the probable contamination as biological or chemical, and to flag suspicious products for further analysis.

FDA will benefit by quick identification of biological or chemical contaminants before food and drugs reach the market. Another benefit will be the increased number of import samples examined for potential contamination. The ultimate goal is to better protect American consumers by more rapidly assessing the threat of foodborne pathogen contamination.

NCTR scientists discovered in FY 2010, a new and potentially patentable technique called Direct Impact Corona Ionization (DICI) mass spectrometry. This technique enables plasma vaporization of whole-cell bacteria to produce information-rich spectral fingerprints that can accurately identify bacteria and could prove invaluable to rapid detection methods.

In 2010, NCTR scientists developed a new classification algorithm for predicting *Salmonella* serotypes using a statistical method called random forest classification. This algorithm presented a new and more accurate approach—as a complement to the current method of cluster analysis—for rapidly predicting the serotypes of unknown *Salmonella* isolates based on the analysis of Pulse Field Gel fingerprinting. This statistical method will improve FDA's ability to rapidly classify novel isolates of foodborne pathogens during outbreaks. The result of this study is newly published in *Journal of Clinical Microbiology* (Sept. 2010, p. 3122-3126).

Antibiotic Resistance – Antibiotic resistance developed from agribusiness use of antibiotics in the food chain is a continuing problem. Since FDA sets antimicrobial drug-residue limits in animal products, NCTR research includes the evaluation of the incidence and mechanisms of drug resistance. This knowledge will help FDA establish better strategies for antibiotic use and help determine the spread of multi-drug resistance and increased virulence of foodborne pathogens and can be used to aid risk assessments.

In FY 2010 NCTR scientists completed a study characterizing the genetic basis for multidrug-resistance in *Salmonella (*enterica serovar Heidelberg strains isolated from human patients). The genetic similarity among strains isolated from human patients, animals, and food indicates the potential for food to serve as a source for multidrug-resistant human infections. Follow-up work on this study aims to determine what factors impact the development and dissemination of antimicrobial resistance in *Salmonella* serovar associated with food animals and human infections.

To aid in risk assessment, scientists from NCTR and ORA's Arkansas Regional Laboratory characterized virulence genes in 81 strains of *Aeromonas veronii* isolated from farm-raised catfish, indicating resistance to multiple antibiotics. These studies illustrate that farm-raised catfish can serve as reservoirs for multiple virulence and antibiotic resistance genes. Although adequate cooking should eliminate pathogenic bacteria, undercooking, or cross-contamination of

utensils during the preparation of catfish, is a concern for spread of sickness and a possible spread of antibiotic resistance.

In addition, NCTR continues to research factors that lead to infections caused by *Salmonella* which cause many cases of serious illnesses each year in the United States. NCTR scientists published a review describing molecular bacteria fingerprinting. These fingerprinting methods can be used as part of a strategy to track the sources of *Salmonella* contamination in the preharvest, poultry-production environment. Improved source-tracking methods and strategies enable FDA investigators to identify the sources of bacterial contamination along the farm-to-fork continuum and suggest intervention strategies. Another research effort aims to develop improved polymerase chain reaction (PCR)-based techniques that will improve monitoring antibiotic resistance among *Salmonella* in imported and domestic food samples. The current official FDA cell-culturing methods are time-consuming and labor-intensive, resulting in slower sampling by regulatory laboratories. The PCR-based methods offer a rapid means to detect *Salmonella* and corresponding antibiotic-resistance markers in food samples simultaneously.

Bisphenol A (BPA) – BPA is an industrial chemical that is used in the production of polycarbonate plastics and epoxy resins widely used in consumer products, including storage containers for foods and beverages, and in medical devices. The primary source of exposure to BPA for the majority of people is likely through the diet, with the highest estimated daily intake of BPA occurring in infants and children. In FY 2010, NCTR conducted research in partnership with the National Institutes of Health to determine if BPA administered to a pregnant nonhuman primate crosses the placenta and exposes the fetus to measurable levels of BPA *in utero*.

The study indicated considerable differences between neonatal rodents and non-human primates, with the primates showing significantly less age-related changes than rats, for internal exposure to the bioactive form of BPA. These studies predict that BPA effects observed in neonatal rodents would be more sensitive indicators of potential toxicity in primates. Data from these animal models will be combined with data from human bio-monitoring data to improve the prediction of internal exposures of target tissues in human infants and fetuses to the bioactive form of BPA (*Toxicology and Applied Pharmacology*, 2010). As a result of this research, FDA will gain an improved understanding of the pharmacokinetic profile of BPA and the associated risk of exposure to BPA in various stages of development.

Performance Measures

The following table lists the performance measures associated with this subprogram.

Measure	Most Recent Result	FY 2010 Target	FY 2012 Target	FY 2012 +/- FY 2010
264101: Develop risk assessment methods and build biological dose-response models in support of food protection. *(Output)*	FY 2010: 1) Developed and validating field-rugged technologies for rapid screening of samples to rule in, or rule out, contamination with select foodborne pathogens applicable to fresh produce (Target Met) 2) Research completed on Bisphenol A (BPA) resulting in the publication of data to improve the prediction of internal exposures of target tissues in human infants and fetuses. (Target Met)	1) Rapid detection toolkits for foodborne pathogens applicable to fresh produce; evaluate in field situations 2) Approved protocols developed and initiated for Bisphenol A (BPA), a component in baby bottles and formula containers	Expand Rapid B system to include new pathogen-specific (PS) assays (tests)	N/A

Enhancing Medical Product Safety
Base Amount: $20,549,001 (All BA)

Public Health Focus

To enhance the safety of medical products, to support FDA's Medical Product Safety priorities, and to support the HHS priority to Improve Health Care Quality and Patient Safety, NCTR scientists conduct research to identify early predictors of toxicity for medical products. NCTR also develops, validates, and provides guidance to FDA medical-product centers for the use of new medical technologies and evaluates the biological effects of potentially toxic chemicals. NCTR research helps FDA to integrate new technologies and standards into the risk-assessment and regulatory-review process at all stages of the product lifecycle.

Public Health Outcome

This research, which provides biomarkers of risk for FDA reviewers and guidance to regulators, will decrease the uncertainty, time, and expense of product development and improve FDA's ability to protect the public health. The

integration of new technologies and standards provides enhanced risk assessment for reviewers and a stronger base for public-health assurance for new products.

Promoting Efficiency

NCTR's research to support the Enhancing Medical Product Safety subprogram has the potential to save lives, increase patients' quality of life, and generate savings for all those who pay the cost of health care. NCTR's bio-imaging capabilities are enhancing the development of noninvasive biomarkers used to track the effects of strokes in a noninvasive manner. Using these biomarkers also offers the possibility of preventing recurring strokes and reducing the need for costly and dangerous surgical procedures.

Liver toxicity is the most likely reason why drugs are withdrawn from the market, and liver toxicity is the second leading cause of acute liver failure in the United States. Liver toxicity has been linked to as many as 1,000 drugs [Abboud and Kaplowitz, 2007]. As a result, NCTR's efforts to create a database of liver toxicity-related information supports the development of predictive tools for identifying liver toxicity throughout the drug-development cycle and reduces the expense (both economically and patient health) of withdrawing drugs after they are on the market.

Imaging– NCTR completed the development of a Bio-Imaging Facility in Fall 2009 that houses the small animal Magnetic Resonance Imaging (MRI), Spectroscopy (MRS), and MicroPET technologies. The instruments in the Bio-Imaging Facility operate at higher-field strengths and with less variability than clinical instruments, providing investigators opportunities for more complex experimental designs and resulting discoveries. As with clinical applications, the noninvasive nature of these technologies enables continued monitoring of animals, providing new possibilities for biomarker discovery for safety and efficacy of FDA-regulated products.

NCTR's bio-imaging capabilities will enhance the development of noninvasive, clinically translatable central nervous system MRI biomarkers of disease progression and drug efficacy. These biomarkers have the potential to serve as important tools that will bring new insight into the step-by-step development of stroke complications — a leading cause of mortality and disability in the U.S. — related to micro-vascular disorders, as well as new safety-assessment tools for therapeutics devised to treat stroke victims.

In addition, NCTR scientists developed a tool to discriminate up to nine categories of brain tissue in Magnetic Resonance Spectroscopy (MRS) images with 96% accuracy. This tool was designed to aid physicians with medical decisions based upon MRS images. The improved MRS-spectrum processing holds promise to aid physicians in the practice of medicine. The process could

reduce the need for surgical procedures, in itself improving the quality-of-life for patients.

NCTR continues to develop novel methods of validating MRI scans by comparing those scans that indicate adverse events, such as tumors, to those caused by benign outcomes such as scarring. For example, follow-up scans performed on patients after brain surgery may reveal some abnormalities, but, at this time, there is no noninvasive method to establish if the tumor has returned or if it is solely the presence of scar tissue. There is an effort underway to locate images from such patients so that model systems can be developed and validated to help distinguish tissue status.

Pediatric Anesthetics – NCTR scientists are evaluating the neurological effects of pediatric anesthetic use in developing nonhuman primates, an animal model closely related to humans. Studies conducted on animals exposed to ketamine, an anesthetic widely used in pediatric medicine, suggest that cell death from ketamine exposure continues much longer than previously thought. Concern over the use of ketamine anesthesia in pediatric medicine increased after animal experiments demonstrated increased neuronal-cell death when exposures occur during periods of rapid-brain development. Completed research demonstrates that Positron Emission Tomography (PET) imaging, in combination with a molecular tracer, provides a minimally invasive approach for monitoring brain-cell death with enough sensitivity to pinpoint different brain areas that are affected. Using a variety of tools, scientists will determine if the use of anesthetics during development is associated with memory and learning deficits or other changes in the central nervous system.

NCTR established a zebrafish facility in Spring 2010 to provide adult fish and embryos for toxicity assessments because they share many developmental and genetic similarities with humans and can provide information on ways to minimize risk associated with the pediatric use of general anesthetics. In addition to zebrafish studies, previous studies with nonhuman primates helped to identify developmental periods during which sensitivity to ketamine, a pediatric anesthetic, is greatest. These non-human primates' offspring will be used for further research on the effects of pediatric exposure to general anesthetics and will result in the development of translatable biomarkers for studying pediatric products.

These research findings will help the medical community understand the relationship between the amount, type, duration, and frequency of pediatric anesthetic use and its adverse effects on children in order to provide rapid screening tests and understand pathways of toxicity and prevention for pediatric anesthetics.

Nanotechnology – Recently, nanomaterials have received enormous national attention as new analytical tools for biotechnology and in the life sciences. Under

certain conditions some of these nanomaterials have been shown to produce toxicity. NCTR scientists are conducting research to determine if manganese or iron nanoparticles cross the blood-brain barrier in rodents and to determine if exposure to these nanoparticles produces neurotoxicity. Data from this study will provide a better understanding of the toxicity of these nanomaterials in products for human use, such as over the counter drugs, cosmetics, or dietary supplements.

Nanomaterials, such as nanoscale zinc oxide and titanium oxide are often found in sunscreen and cosmetics. These nanomaterials could penetrate the skin or be absorbed in the gut following ingestion. Studies at NCTR have shown that nanoscale titanium dioxide does not penetrate the skin of mice and rabbits; however, insufficient information exists on the skin penetration of nanoscale zinc oxide. Very limited information on the uptake of nanoscale materials from the gut exists. Studies are focusing on the gut uptake of nanoscale zinc oxide to assess the safety of these materials. In addition, there is potential that externally applied cosmetics containing nanoscale materials could impact the microbial ecology of the skin, which may affect human health by breaking the permeability barrier encouraging bacterial growth on the skin. NCTR will evaluate the effect of cosmetics and sunscreens on model microorganisms that are representative of the human skin microbiota to evaluate the potential risk of skin exposure to nanomaterials. This research will provide the scientific underpinnings necessary to determine the potential health effects of skin exposure to nanomaterials.

In addition to cosmetics, the greatest risk of consumer exposure to nanoparticles is from food packages containing nanomaterials, due to potential migration of nanoparticles into food or drinks. Nanoparticle-migration data are not available despite the fact that a number of nanomaterials are already available for use. Silver nanoparticles are a high priority because of their applications as antimicrobial agents in food packages. Developing methods to measure the extent of nanosilver migration from food-contact nanomaterials will allow FDA to determine the magnitude of the problem. Since the use of food-contact nanomaterials has been increasing in the last ten years, the risk associated with the migration of nanoparticles into the food should be studied.

To strengthen FDA's nanotechnology product-evaluation capability, in FY 2010 the NCTR/ORA Nanotechnology Core Facility was opened, equipped, and staffed with a Senior Electron Microscopy Technician and a Staff Fellow with expertise in nanotechnology. The Nano Facility is providing support to FDA through materials characterization — external techniques to probe into the internal structure and properties of a material — analytical support, and electron microscopy support for a broad range of nanomaterial studies. In FY 2010, Standard Operating Procedures were established for:

1) Transmission Electron Microscope (TEM)
2) tissue preparation for TEM

3) particle-size determination with more SOP development in progress.

The Nano Facility is supporting various collaborative studies with FDA/ORA, National Institute of Environmental Health Sciences/National Toxicology Program, National Cancer Institute/Nanotechnology Characterization Laboratory, and the United States Air Force on quantification and migration of nanosilver, particle-size determination of nanosilver, and toxicity of nanomaterials on cultured brain cells and on cells used in genotoxicity assays. The results of a study on nano- and submicron-particles of titanium dioxide contained in sunscreens was published in *Toxicological Sciences,* 2010. The results suggest that use of the sunscreens does not result in internal exposure to the nano- and submicron-particles of titanium dioxide

Nanotechnology research will aid in the development of guidelines for the safe and effective use of these materials in drug products, devices, foods, cosmetics, and dietary components. By continuing nanomaterials research, FDA will have a better understanding of the consequences of human exposure to nanoscale materials.

Liver Toxicity – Since both prescription drugs and over-the-counter medication can contribute to this problem, liver toxicity is of great concern to FDA. To address this public-health issue, a Liver Toxicity Knowledge Base (LTKB) is being developed at NCTR to provide a resource for FDA to improve the safety of drugs, biologics, and dietary supplements. In 2010, NCTR scientists developed a set of criteria to select drugs for the Liver Toxicity Knowledge Base (LTKB) project and collected risk factors and mechanistic data for them from literature. A high-content assay was performed on these drugs. In addition, a systematic approach to characterize the potential risk of liver injury of these drugs was developed for this project. LTKB is a content-rich resource being developed to aid understanding of liver toxicity and enable the development of predictive tools for identifying liver toxicity issues along the various stages of drug development.

In FY 2010, NCTR submitted a manuscript on drug-induced liver injury (DILI) by sex. While it is known that DILI is more common in females, it is unclear how common this potential sex-based sensitivity may be and the contributing factors. Scientists analyzed preclinical, clinical, and post-market reports to determine the weight of evidence in support of sex-biased sensitivity to DILI. The analysis indicated that care must be taken when interpreting the “apparent” female-biased DILI since the actual number of patients exposed to drugs is difficult to estimate by sex. In addition, the pre-clinical data has limited ability to predict sex-biased DILI in humans. Nevertheless, several significant factors were found to contribute to sex-biased DILI including drug type, age, and injury type—in descending order of influence.

In addition, the Hepatotoxicity Working Group formed by NCTR with experts from FDA, pharmaceutical industry, and academia continue to identify research needs

surrounding drug-induced liver injury. NCTR will collaborate with the working group and other government agencies to conduct studies to identify novel biomarkers for liver toxicity. Liver toxicity is usually investigated using animal-based studies which, unfortunately, fail to detect all compounds that induce human adverse events and do not provide detailed toxicity information. NCTR will supplement animal testing with a battery of *in vitro* and "omics" technologies. The information and the biomarker models derived from this research will be useful when liver toxicity issues arise during the various stages of the FDA regulatory review process.

Bioinformatics Infrastructure – Pharmacogenomics (PGx), an emerging scientific field focused on clinical and safety biomarker identification, is identified in the Critical Path Initiative as a major opportunity for advancing medical product development. PGx requires a bioinformatics infrastructure to review and understand how sponsors reach their biological conclusions, to ensure the incorporation of PGx data into regulatory processes and to realize benefits of PGx for public health.

NCTR-developed ArrayTrack™ — the integrated DNA microarray data management, mining, analysis, and interpretation software system — allows for the addition of new capabilities to handle priorities and evolving technologies and can be used to support Pharmacogenomics. Initially ArrayTrack™ was used predominately to analyze and manage large amounts of DNA data; however, it is being expanded to facilitate the review of other types of data. ArrayTrack™ now includes a Microbial Library and new data processing and visualization tools. The Microbial Library currently holds 270,000 gene records from 84 strains, including *Escherichia coli*, *Salmonella enterica*, *Shigella spp.*, and *Vibrio spp*., which are common foodborne pathogens. These additions facilitate the analysis of data generated by NCTR researchers and custom analytical tests developed at FDA's Center for Food Safety and Nutrition and USDA, demonstrating ArrayTrack™'s use in microbial genomics research. The ArrayTrack™ platform facilitates rapid identification of intestinal pathogens and their genetic traits including antimicrobial resistance, virulence, and DNA fingerprints in outbreak investigations. In FY 2010, NCTR also enhanced the ArrayTrack™ tool by adding a protein and metabolite panel and a Gene Ontology for Functional Analysis (GOFFA) library, as well as a Support Vector Machine for outcome prediction and data mining.

Performance Measures

The following table lists the performance measures associated with this subprogram.

Measure	Most Recent Result	FY 2010 Target	FY 2012 Target	FY 2012 +/- FY 2010
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)*	FY 2010: 1) Developed drug selection criteria for the Liver Toxicity Knowledge Base, collected data, performed high-content assays, and developed a systematic approach to characterize the potential risk of liver injury of these drugs. Tool is being piloted. (Target Met) 2), Established zebrafish facility for toxicity assessments and have eliminated some potential candidates, narrowing search and evaluating data to identify translatable biomarkers. (Target Met)	1) Create a demonstrable tool to use in the drug-review process based upon the liver toxicity knowledge base 2) Develop translatable biomarkers for studying pediatric products (such as ketamine, methylphenidate, etc.)	1) Establish an imaging consortium of scientific experts from NCTR, CDER, and from other government agencies, industry, and academia to refine the imaging tools 2) Determine pathways of toxicity and preventive strategies for pediatric anesthetics using a high-speed, high-volume method (zebrafish) 3) Build a knowledge base to annotate existing drug-risk factor associations of immune-related drug reactions	N/A
263102: Develop computer-based models and infrastructure to predict the health risk of biologically active products. *(Output)*	FY 2010: Molecular signature and biomarker functions developed in ArrayTrack™ to support VXDS (Target Met)	Develop molecular signature and biomarker modules in ArrayTrack™ to support VXDS	Develop 3D/4D Quantitative Spectrometric Data-activity Relationship (QSDAR) models for predicting endocrine disruptor activity	N/A
263201: Develop science base for supporting FDA regulatory review of new and emerging technologies. *(Output)*	FY 2010: Established and implemented three SOPs for research protocols to detect nanoscale materials in FDA-regulated products in collaboration with ORA/ARL. (Target Met)	Establish and implement standard operating procedures (SOP) in research protocols for detection of nanoscale materials in FDA-regulated products in collaboration with ORA/Arkansas Regional Laboratory (ORA/ARL)	Develop new characterization methods for nano-based zinc oxide within FDA-regulated products	N/A

<u>Information Technology Investments</u> – National Center for Toxicological Research Activities (Base Amount displayed as a non-add item: $7,676,000)

The ongoing modernization and enhancement of the FDA information technology (IT) infrastructure and systems is creating a robust foundation to enable interoperability of regulatory data sharing across the FDA program areas. This allows FDA to transform nearly every aspect of its operations and regulatory duties. FDA has agency-wide costs associated with the operation and maintenance of shared IT infrastructure which includes data centers, security, telecommunication networks, and help desk functions. In addition, each center and office has program specific IT systems and FDA also has a number of enterprise systems ranging from improving the pre-market review process for all regulated products to post-market surveillance, including adverse event detection and future scientific computing capabilities.

Science is the foundation of the FDA regulatory decision-making process and is vital to FDA's role in protecting and promoting the health of American consumers. In addition to investments in IT infrastructure, unique center-specific systems, and enterprise-wide systems, the following are examples of IT development efforts to enhance the efforts of interdisciplinary scientists as they conduct peer-reviewed research essential to identifying health and safety issues related to new and existing FDA-regulated products. Some examples include advances in IT that will provide the necessary tools to allow electronic-data retrieval through expanded network and data-storage capabilities. Initiatives such as the Janus project will provide FDA with a standardized data warehouse with linked analytical tools. These initiatives will enrich the regulatory desktop environment by making structured scientific data and knowledge from external and internal sources readily available for the conduct of science-based risk/benefit assessments. Additionally, identification of IT platforms and tools, including innovative analytical tools and science algorithms–mathematical procedures–will enable computational sciences to address the critical-path goal of personalized nutrition and medicine.

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Five Year Funding Table with FTE Totals

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	User Fees	FTE
FY 2007 Actual	$42,056,000	$42,056,000	$ 0	183
FY 2008 Actual	$44,443,000	$44,443,000	$ 0	192
FY 2009 Actual	$55,720,000	$55,720,000	$ 0	217
FY 2010 Actual	$58,531,000	$58,531,000	$ 0	246
FY 2011 Continuing Resolution	$58,745,000	$58,745,000	$ 0	246

Summary of the Budget Request

The FY 2012 budget request for the National Center for Toxicological Research is $60,294,000 supporting 215 FTE. The amount is an increase of $1,549,000 above the FY 2010 Enacted.

The base funding for the National Center for Toxicological Research Program is $58,745,000, which supports research in the following three subprogram areas:

- Personalized Nutrition and Medicine
- Strengthen Surveillance and Risk Analysis
- Enhancing Medical Product Safety.

Within these subprogram areas, NCTR conducts research on the risks and benefits of products — and thereby advances the FDA mission of protecting patients and consumers — across the full spectrum of products that FDA regulates: animal and human drugs, devices, cosmetics, biologics and tissues, tobacco and foods. The goal of these programs is to enable FDA to make sound, science-based regulatory decisions and improve the health of the American people.

Personalized Nutrition and Medicine

Center Activities (Base Amount: $24,249,936)

Initiatives None requested.

Strengthen Surveillance and Risk Analysis

Center Activities (Base Amount: $13,946,063)

Initiatives

Transforming Food Safety and Nutrition Initiative: Expanding Laboratory Capacity and Capability for Food Safety (+$414,000 BA; 1 FTE)

Many hazardous chemicals go undetected in food samples due to:

- the highly specific nature of current chemical testing methods
- an insufficient number of field portable and hand-held instrumentation devices

- an inadequate and understaffed laboratory infrastructure to assist FDA in preventing and responding to foodborne contamination.

Developing new, rapid-detection devices and methods will:

- shorten the response time
- increase the number of samples analyzed
- identify chemicals that might otherwise go undetected
- lead to a low cost rapid screen for food contamination.

The ability to more rapidly identify contamination will protect the public health by reducing the number of foodborne illnesses.

Using these funds, FDA/NCTR will support one FTE and will build on existing capacity and capability by:

- developing and deploying rapid detection tests
- supporting the FDA Analytical Tools initiatives by identifying new biomarkers and metabolomic profiles
- developing *in vitro* assays for measuring toxicity and replacing animal models.

Enhancing Medical Product Safety

Center Activities (Base Amount: $20,549,001)

Initiatives

FDA Regulatory Science and Facilities Initiative: Nanotechnology (+$1,700,000; 4 FTE)

For this Nanotechnology Initiative, NCTR will conduct activities that support the following FDA-wide priorities:

- laboratory and product testing capacity
- scientific staff development and training
- collaborative and interdisciplinary research to address product characterization and safety.

Together, these priorities will better enable FDA to bring benefits of nanotechnology to bear while reducing risks.

BA Increase for Pay Costs: +$134,000 (all Center)

Contract and Administrative Savings (Total Program: -$699,000)

The request for $60,294,000 in total budget authority for the National Center for Toxicological Research also reflects a contract and administrative savings reduction of -$699,000.

Center Activities

Initiatives

Administrative and Contract Savings Initiative (-$699,000)

NCTR will achieve contract savings by reviewing contracts for research support and identifying activities that NCTR workforce can perform.

NCTR Program Activity Data (PAD)

The following table lists the NCTR Program Activity Data (PAD).

NCTR Workload and Outputs	FY 2010 Actual	FY 2011 Estimate	FY 2012 Estimate
RESEARCH OUTPUTS			
Research Publications	165	160	165
Scientific Presentations	190	178	175
Patents (Industry)	6	6	5
LEVERAGED RESEARCH			
Federal agencies (Interagency Agreements)	4	8	5
Nongovernmental organizations	15	20	16
ACTIVE RESEARCH PROJECTS			
Personalized Nutrition and Medicine	64	60	60
Strengthen Surveillance & Risk Analysis	42	42	42
Enhancing Product Safety	55	50	54
Total Active Research Projects	***161***	***152***	***156***