NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

Introduction

FDA's National Center for Toxicological Research summarizes the budget program requirements that justify a $36,455,000 request for FY 2008. The National Center for Toxicological Research narrative has four sections:

- summary of FDA's program resources, historical funding, and FTE levels
- description of program functions of the National Center for Toxicological Research
- effects of the full year FY 2007 continuing resolution on the National Center for Toxicological Research
- description of the program resources changes, base resource activities, program accomplishments, program activity data, and performance plan analysis.

The National Center for Toxicological Research funding table shows a three year span of program level resources, budget authority resources, and proposed user fees enacted in FY 2006, displayed in the FY 2007 President's Budget and FY 2007 Continuing Resolution, and proposed in the FY 2008 budget request.

	FY 2006 Actuals	FY 2007 Continuing Resolution	FY 2007 President's Budget	FY 2008 President's Budget	Increase or Decrease
Program Level	**$40,739,000**	**$40,740,000**	**$34,240,000**	**$36,455,000**	**$2,215,000**
FTE	**190**	**180**	**183**	**183**	**0**
Budget Authority	**$40,739,000**	**$40,740,000**	**$34,240,000**	**$36,455,000**	**$2,215,000**
Pay Increase	--	--	--	*$519,000*	*$519,000*
Food Safety	--	--	--	*$500,000*	*$500,000*
Rent and Rent Related	--	--	--	*$1,196,000*	*$1,196,000*
Total FTE	**190**	**180**	**183**	**183**	**0**

The historical funding and FTE levels table shows a five year history of program level funding, budget authority funding, user fee funding, and program level FTE.

Historical Funding and FTE Levels

Fiscal Year	Program Level	Budget Authority	User Fees	Program Level FTE
2004 Actuals	$39,869,000	$39,869,000	--	207
2005 Actuals	$40,206,000	$40,206,000	--	187
2006 Actuals	$40,739,000	$40,739,000	--	190
2007 Continuing Resolution	$40,740,000	$40,740,000	--	180
FY 2007 President's Budget	$34,240,000	$34,240,000	--	183
2008 President's Budget	$36,455,000	$36,455,000	--	183

Statement of the Budget Request

The National Center for Toxicological Research (NCTR) requests $36,455,000 to conduct mission-critical research activities:

- conduct peer-reviewed research that develops a scientific basis for regulatory decisions
- perform integrated research to link laboratory discovery to bedside application
- foster interagency, academic, and industrial collaborations supporting safety assessment and risk decision-making.

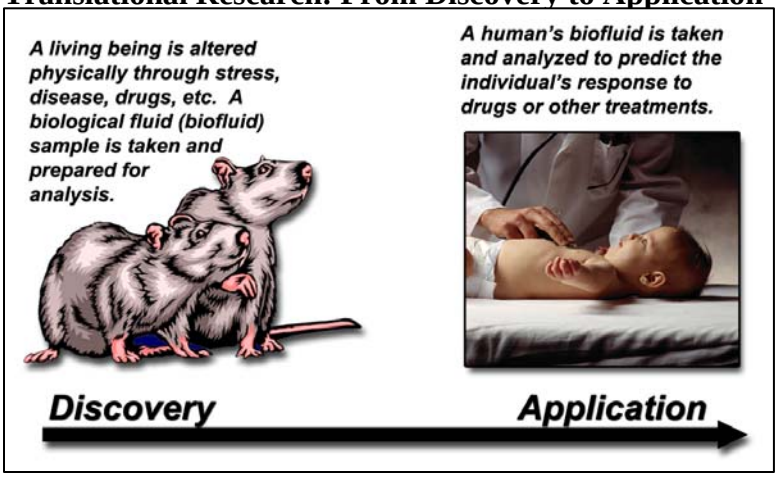
Program Description

An Executive Order in January 1971 established the NCTR as a scientific resource, owned and managed by FDA, to conduct translational research vital to the mission of protecting the public health. Through the efforts of highly trained scientists and contract support staff, NCTR conducts fundamental and innovative laboratory research:

- develops scientific processes to advance FDA towards personalized medicine (individualized therapy and disease susceptibility)
- identifies early predictors of risk of toxicity of regulated products
- develops, validates, and provides guidance for the regulatory use of new technologies
- provides regulatory tools that facilitate premarket review, postmarket safety assurance, and risk-based product safety decisions

- evaluates the biological effects of potentially toxic chemicals or microorganisms
- provides key research data for high priority safety issues
- provides research for food safety and food defense.

Translational Research: From Discovery to Application



NCTR translational research closes the gap between discovery and practical application (as depicted in the graphic to the right). This research determines the safety of products for patient use. For example, NCTR scientists, working with their CDER colleagues, verified that ketamine, a pediatric anesthetic, induces neural cell death in developing nonhuman primates. Studies are determining exposure times and durations to establish safe anesthetic exposure scenarios and develop countermeasures to block toxicity.

NCTR's integrated research approach combines expertise from FDA Centers, educational facilities, and industries to address regulatory review needs. As described below, NCTR research provides cutting-edge technology for FDA reviewers and solutions to complex safety issues.

Innovative Technologies

NCTR launched the "Critical Path to Medical Product Development" initiative to reverse the unfavorable trends of slow new drug development and high numbers of drug recall. NCTR scientists worked with proprietary data from regulated industry to develop new tools to provide faster and novel insights into drug safety and efficacy.

NCTR conducts research at an FDA-owned facility in Jefferson, Arkansas. NCTR is co-located with ORA's Arkansas Regional Laboratory on the campus of the Jefferson Laboratories of the FDA in Jefferson, Arkansas.

Jefferson Laboratories of the FDA

Effects of Full Year FY 2007 Continuing Resolution

The analysis in this justification assumes funding levels for FY 2007 based on the enactment of the President's FY 2007 budget for NCTR. For comparison purposes, FDA budget tables also include a column in the FDA budget tables that reflects an FY 2007 Continuing Resolution (CR) level in the event that Congress enacts this level of appropriations for the remainder of FY 2007.

If FDA receives the CR rather than the FY 2007 President's budget request, this will have the following impact on FY 2008 performance for NCTR:

- reduced number of canceled or delayed research projects in FY 2007 resulting in an increase in data, methods, and publications useful in regulatory review and decision making in FY 2008

- retention of current technical and scientific staff, reducing lost expertise that would take years to recover.

Program Resource Changes

Pay Increase: +$519,000

The FDA request for pay inflationary costs is essential to accomplish our public health mission. Eighty-three percent of FDA's budget supports the agency workforce. Of this, payroll costs account for over sixty percent of our total budget. The increase will allow FDA to maintain staff levels, including a national cadre of specially trained scientific staff. Maintaining the FDA workforce provides stability for the organization and allows FDA to maintain the current level of coverage for its premarket and postmarket activities. Without these funds, FDA must reduce FTE levels in order to have adequate resources to cover its payroll, which will lead to corresponding reductions in programs that protect public health. The total request for cost of living pay increases in FY 2008 is $21,773,000. The NCTR portion of this increase is $519,000**.**

Other Rent and Rent Related: +$1,196,000
The request helps address NCTR's costs for mandatory items such as security and utilities and reduces the need for charging mandatory costs to NCTR's food safety, medical product safety, and other high-priority public health activities.

Strengthening Food Safety: +$500,000
FDA proposes a total of $10,644,000 for food safety activities, $500,000 of which is for the NCTR, to enhance FDA's ability to help industry mitigate the risks of increased foodborne outbreaks. The resources would also improve FDA's ability to protect the public health by enhancing our ability to respond to possible foodborne outbreaks. NCTR would continue developing rapid field-compatible methods to help determine the underlying cause of foodborne contaminations. Funds would also allow NCTR to develop a genomic database to identify and assess biological threat of foodborne pathogens in food and feed products that can be applied to the development of risk-based strategies to address food safety threats.

Justification of Base

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 the American people. Research performed at NCTR targets four program areas:

Critical Path to Personalized Nutrition and Medicine

This program area facilitates the advancement toward personalized nutrition and medicine. The goals are to define and characterize individual responses to regulated products and to assess innovative products for possible use. This increases the predictability and efficiency of product development to address unmet public health needs.

Translational and Applied Toxicology

The translational and applied toxicology program area performs customized bioassessments of regulated products. The goals are to address emerging scientific issues and to fill the knowledge gaps required for the comprehensive risk evaluation that is essential to regulation. This program provides data for the formulation of quantitative safety assessment for humans, thus ensuring the safety of regulated products. This program bridges the gap from the scientific bench to the patient's bedside.

Food Defense and Food Safety

The food defense and food safety program area facilitates the detection of both naturally occurring and intentional contamination of the food supply or the environment. Studies lead to the development of rapid, field-ready standards for the early detection of microbial or chemical threats to the food supply, thus reducing exposure to toxins and ensuring timely intervention strategies.

Biomarker Identification for Regulated Products

The biomarker identification area conducts safety assessments for regulated products in order to provide accurate and reproducible techniques. Techniques using new technologies, supported in part through collaboration with industry and academia, speeds the process of regulatory decision-making while increasing confidence and predictability. The overall goal is to decrease the uncertainty, time, and expense of product development.

The four research program areas at NCTR support the FDA strategic goals identified in the table below in six ways:

1. developing safer and more effective therapies that replace one-size-fits-all drugs with treatments that focus on specific population needs

2. understanding how individual attributes affect responses to drugs, foods, nutrients, and dietary supplements

3. developing improved tools and methods to manage or assess risk associated with the products regulated by FDA

4. building the capability to identify, assess, and reduce food-related health threats

5. providing technical expertise for the interpretation of data and the development and harmonization of guidelines

6. leveraging NCTR's resources and scientific expertise with other agencies (through Interagency Agreements) and non-government groups (through Cooperative Research and Development Agreements) to support FDA's critical research needs.

NCTR Program Support of FDA Strategic Goals

The table below illustrates how NCTR's activities support FDA's strategic goals.

	FDA Strategic Goals		
	Increase Access to Innovative Products and Technologies to Improve Health	Improve Product Quality, Safety and Availability Through Better Manufacturing and Production Oversight	Transform Administrative Systems and Infrastructure to Support FDA Operations
Program Area			
Critical Path to Personalized Nutrition and Medicine	X		X
Translational & Applied Toxicology	X		X
Food Defense & Food Safety		X	X
Biomarker Identification for Regulated Products		X	X

Critical Path to Personalized Nutrition and Medicine

This program develops new scientific tools and biomarkers to expedite FDA's Critical Path research in the areas of medical product discovery, development, and assessment. NCTR continues to use new technologies to study the risk associated with the interactions of regulated compounds and products with the human body. Project results provide a scientific basis for FDA regulatory standards and decrease time and expense of product development.

Base resources used by this program enable NCTR to conduct research on key activities using the most up-to-date scientific technologies:

- advancing of the use of genomics, proteomics, metabolomics, and bioinformatics technologies in medical product development and personalized medicine

- participating as essential partners, in the ongoing Voluntary Genomic Data Submission (VGDS), a process vital to developing personalized medicine and enhancing product development

- directing the continued partnership with other FDA Centers and microarray industry providers in the Microarray Quality Control (MAQC) project establishing standards for assessing and evaluating different microarray platforms

- providing software systems and analysis capability to manage and integrate data from "omics" technologies with traditional toxicological data

- enhancing ArrayTrack™ by expanding it to include a module for analyzing genomic data; ArrayTrack™ is NCTR-developed data management and analysis software used to store and analyze the thousands of data points generated by a single microarray experiment.

Translational and Applied Toxicology

NCTR's research improves product quality and enables scientists to predict the toxicity of new drugs more efficiently. FDA's product centers employ this information for premarket application review and product safety assurance; thereby, managing public health risk. Base resources enable NCTR researchers to use translational research:

- developing methods to enhance scientific understanding of acute and chronic liver, kidney, nervous system, and cardiovascular diseases

- determining the impact of selected genomic markers on colorectal cancer (CRC) cases by identifying an individual's risk of getting CRC, their prognosis after diagnosis, and the effectiveness of their treatment.

Food Defense and Food Safety

NCTR uses resources for this program to develop methods to assess or manage risks associated with products that have been adulterated, intentionally contaminated, or otherwise found to be detrimental to human health. NCTR continues to support the Department's goal of enhancing the ability of the Nation's health care system to respond to bioterrorism and other public health challenges. NCTR conducts food defense and food safety research:

- developing methods to rapidly distinguish bioterror hoax material in samples containing pathogenic and non-pathogenic bacteria
- developing methods and recommending industry guidelines to evaluate the safety of antimicrobial agents on human health
- developing intervention strategies to reduce frequency of multi-drug resistant microorganisms and key pathogens in the U.S. food supply
- developing, validating, and sharing new technology and improved commercial test kits for detection of foodborne pathogens, select agents, and toxins in complex food matrices.

Biomarker Identification for Regulated Products

Base resources enable NCTR to conduct research that establishes the safety of products commonly used by the public:

- Using base resources, NCTR can determine exposure times to establish safe anesthetic exposure scenarios for ketamine, a commonly used pediatric anesthetic that induces neuronal cell death observed in the developing nonhuman primate.
- NCTR can study and address the potentially hazardous effects of sunlight on products used by the public, such as *Aloe vera* products and tattoo ink ingredients.
- NCTR can determine the safety of nanotechnology products (miniscule particles that measure less than 100 nanometers) and assist the FDA in its evaluation of nanotubes (extremely small tubes made from pure carbon) as safe delivery platforms for drugs.

Research, Development, and Evaluation

Congressional Appropriation Report 109-255 directed FDA to include additional justification on its research, development, and evaluation (RD&E) activities. In response to this report language, FDA is providing explanatory paragraphs detailing

each program's RD&E activities. Because NCTR performs RD&E as its main activity, the justification of base also serves as the RD&E paragraph for this program narrative.

Selected FY 2006 Accomplishments

Critical Path to Personalized Nutrition & Medicine

FDA envisions clinical tests for identifying patients most likely to benefit from a particular drug or most likely to have an adverse reaction to a specific drug. NCTR conducts a broad range of studies involving traditional, new, and comprehensive systems toxicology assessments that characterize biomarkers of disease risk and status that aid the FDA in assessing risk for use of treatments in a personalized medicine paradigm. In FY2006, NCTR conducted many studies to advance personalized medicine:

- completed phase I (collaboration of 151 scientists from 51 organizations) of the Microarray Quality Control (MAQC) project, which documented that microarray technology provides the reliability and consistency necessary for regulatory submissions, and was summarized in the September 2006 issue of *Nature Biotechnology*

- initiated phase II of the MAQC project designed to reach consensus on procedures for evaluating clarifiers (predictive signatures of microarrays) to enhance the review process

- released GOFFA (Gene Ontology for Functional Analysis), a new module of ArrayTrack™, the NCTR-developed software for storing and analyzing microarray data. GOFFA uses gene ontology (characterization of genes and gene product attributes) for studying data from genomics and proteomics technologies

- developed best practices guidelines for submitting genomics data to FDA through active participation in the Voluntary Genomics Data Submission (VGDS) process

- interpreted gene expression profiles and their relationship with the carcinogenic potential of the nutritional supplements comfrey and aristolochic acid using the ArrayTrack™ database

- completed preliminary studies demonstrating that the newly NCTR-created transgenic mouse model is effective for screening antiretroviral drugs administered through the placenta for potential carcinogenicity

- demonstrated that dietary components found in the cabbage, turnip, and mustard families change the DNA methyltransferase enzymes in pancreatic cancer, which affects the effectiveness of chemotherapeutic drugs

- demonstrated an association between dopamine gene expression and neurotoxicity induced by 3-NPA (a foodborne contaminant) and methamphetamine (a regulated product and drug of abuse)

- examined the relationship between exposure to type 2 diabetes drugs, gene expression patterns, and toxicity and determined that microarray analysis, together with toxicological observations, is a tool for ranking drugs for liver toxicity

- developed classification algorithms to facilitate the use of genomic biomarkers for clinical assignment of therapies on an individual-patient basis advancing movement to more personalized medicine.

Translational & Applied Toxicology

An important function of the FDA is to identify risks associated with the use of medical products and devices, improve the translation of preclinical data to advancing clinical care, and reduce the occurrence of adverse events. NCTR develops tools and methods to manage or assess risk associated with regulated products. These tools involve coordinated interdisciplinary research to identify biomarkers of toxicity and exposure in differing test species. NCTR researchers created and made available many such tools in FY 2006:

- developed a pharmacodynamic assessment model for acrylamide that incorporates rodent toxicokinetic and biomarker data and predicts steady state human DNA adduct levels associated with dietary consumption of acrylamide

- developed specific gene expression platforms to determine if a neurotoxicant (either amphetamine or acrylamide) produced neurotoxicity within a specific brain region

- developed an analytical method to study diet-drug interactions between soy isoflavones (estrogen-like substances) and tamoxifen (a drug used to treat cancer) with respect to changes in breast cancer incidence/survival

- published an internationally harmonized guidance for the interpretation of data from the *in vitro* mammalian gene mutation assay used in preclinical safety evaluation

- provided training for CDER reviewers on the proper interpretation of data from the *in vitro* mammalian mutation assay

- developed a method for simultaneous analysis of eight neurotransmitters and metabolites (dopamine, dopac, 3MT, HVA, Serotonin, 5HIAA, epinephrine, and norepinephrine) and applied the method to test brain samples taken from rats exposed to acrylamide (a chemical produced when some food products, such as potatoes, are cooked at high temperatures)

- determined from preliminary data, that photochemical properties induced by ultraviolet irradiation of *Aloe vera* plant components and retinyl palmitate, two very popular and widely used cosmetic ingredients, may enhance sensitivity to cancer producing ultraviolet light.

Food Defense & Food Safety

To address research needs and build the capability to assess and reduce food-related health threats, NCTR researchers evaluate regulatory issues of food safety, conduct multidisciplinary studies to develop risk assessment methods, and develop biological doses-response models. NCTR develops and validates new technologies for the rapid identification of contaminants and develops intervention strategies to reduce threats to human health. NCTR researchers made advancements in food defense and food safety:

- developed and tested an assay to test foods for the bioterrorism agents ricin and abrin, including heated foods such as infant formula
- collaborated with the USDA to study the survivability of *Bacillus anthracis* bacteria in liquid and processed eggs and developed a risk assessment model to assess the threat of eggs as a potential source of biological contaminant with anthrax
- studied the traits of *Salmonella* serovars (subdivisions of a species that is different from other strains) in poultry flocks to identify the source of bacterial origins, describe the transmission pathways, and establish preharvest control of foodborne pathogens in the "farm-to-the-fork" continuum
- developed a method to rapidly identify bacterial pathogens using pyrolysis (the chemical decomposition by the action of heat) and mass spectrometry methods
- developed a microarray method to screen 131 antibiotic resistance markers for most of the antibiotics used by the National Antibiotic Resistance Monitoring System
- isolated tetracycline-resistant *Aeromonas* spp. bacteria strains from farm-raised catfish and characterized the strains using biochemical and molecular methods.

Biomarker Identification for Regulated Products

NCTR conducts research that leads to the identification of biological markers, or biomarkers. These biomarkers are early indicators of toxicity or disease, and may be biological, molecular, or physical. NCTR conducts the following biomarker identification research:

- utilized *in vitro* and *in vivo* methods in parallel to study the neurotoxicity of ketamine (a pediatric anesthetic agent). The use of two species allowed detailed interspecies comparison of neurotoxic mechanism
- developed a procedure to determine if exposure of nonhuman primates to methylphenidate (medicine often used to treat attention deficit hyperactivity disorder) results in genetic or cognitive function damage.

NCTR
Program Activity Data

PROGRAM WORKLOAD AND OUTPUTS	FY 2006 Actuals	FY 2007 Continuing Resolution	FY 2007 President's Budget	FY 2008 President's Budget
Research Publications[1]	153	215	215	116
Scientific Presentations	285	175	150	50
Patents (Industry)	6	5	5	2
Leveraged Research				
Federal agencies (Interagency Agreements)	8	7	7	5
Nongovernmental organizations (CRADA)	9	11	11	7
Active Research Projects[2]				
Critical Path to Personalized Nutrition & Medicine	82	78	64	51
Translational and Applied Toxicology	62	60	55	35
Food Defense & Food Safety[3]	36	36	34	28
Biomarker Identification for Regulated Products	11	8	5	4

[1] The NCTR research process typically requires 12-24 months to complete. An additional 6-12 months is devoted to completing articles for publications. Therefore, projects begun in FY 2005 should be published in FY 2007. Due to the redeployment of resources in the FY 2007 budget, the number of new projects began to decline in FY 2006. Therefore, the number of publication in FY 2008 will continue to show a decline. With the additional funds requested in the FY 2008 budget, an increase in the number of publications should begin in FY 2009 and continue into FY 2010.

[2] The reduction of projects in FY 2008 is a result of the decline in the number of new projects started in FY 2006 and projected for FY 2007 due to redeployment of resources in FY 2007. New projects usually require approximately 9-12 months to complete the planning, development, and peer-review processes required prior to beginning the research. With the additional funds requested in the FY 2008 budget, an increase in the number of research projects should begin in FY 2009 and continue into FY 2010.

[3] Includes one study supporting Pandemic Flu initiative.

Performance Analysis

During the latest performance period (FY 2006) the National Center for Toxicological Research successfully met all of the targets for NCTR's four performance goals. For more information about these performance goals and results, please see the Performance Detail section.

NCTR continues to support the Agency's counterterrorism efforts by conducting research to protect the Nation's food supply from a terrorist's attack. NCTR has set ambitious targets in support of these efforts.