

## NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

(Dollars in Thousands)	FY 2015 Final	FY 2015 Actuals	FY 2016 Enacted	FY 2017	
				President's Budget	+/- FY 2016
National Center for Toxicological Research (BA Only).....	63,331	63,312	63,331	60,277	-3,054
FTE.....	287	276	276	276	---

**Authorizing Legislation:** 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; FDA Food Safety Modernization Act (P.L. 111-353)

**Allocation Methods:** Direct Federal/Intramural

### **PROGRAM DESCRIPTION AND ACCOMPLISHMENTS**

The National Center for Toxicological Research (NCTR) was established in 1971. As a national scientific resource, NCTR conducts peer-reviewed research to advance scientific approaches and tools required to support public health and to improve FDA’s ability to assess the safety of regulated products.

NCTR supports FDA’s strategic priorities to advance regulatory science and engage globally to encourage the implementation of science-based standards. In support of FDA’s strategic goals to Enhance Oversight of and Improve Access to FDA-regulated products, NCTR enhances FDA’s basis for science-based regulatory decisions by conducting collaborative research to:

- identify adverse effects earlier in product development
- provide strategies to reduce and rapidly detect contaminants in FDA-regulated products
- use biomarkers – biological indicators – to promote individualized precision medicine
- accelerate FDA’s capability to manage and analyze research data using bioinformatics
- understand the risks and benefits of nanoscale materials used in FDA-regulated products
- reduce costly and dangerous surgical procedures by expanding imaging capabilities
- expedite the translation of scientific advancements to regulatory application.

The following selected accomplishments demonstrate NCTR’s delivery of its regulatory and public-health responsibilities within the context of current FDA Strategic Priorities and Goals.<sup>75</sup>

#### **Enhance Oversight**

NCTR’s research allows FDA to use regulatory science to inform standards development, analysis, and decision-making for the safety of FDA-regulated products. NCTR conducts a full range of studies in support of FDA’s product portfolio as seen in the illustrations below. Within the Goal of Oversight, NCTR conducts research in Pediatric Medicine along with Antimicrobial Resistance and the Human Microbiome that also address the FDA Strategic Priority on Regulatory Science.

#### **Pediatric Medicine**

Advancements at NCTR’s bio-imaging facility allow FDA to gather information not previously obtainable to help the medical community understand pediatric-anesthetic use and its adverse

<sup>75</sup> More information on NCTR Research Accomplishments can be found at:  
<http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/ResearchAccomplishmentsPlans/default.htm>

effects on children. These effects are assessed using minimally invasive imaging technology, allowing visualization of biological processes in “real time,” with as little interference as possible with life processes. Four manuscripts published in FY 2015 describe researchers’ findings on this topic. This research is aimed at the translation of these imaging technologies from the laboratory animal to the clinical setting to reduce adverse effects to children.

In FY 2015 NCTR investigators, in collaboration with UAMS and the Sanford-Burnham Medical Research Institute, demonstrated significant changes and nerve cell damage in brains of infant nonhuman primates exposed to the anesthetic sevoflurane for prolonged periods. This study found potentially sensitive indicators of brain status after anesthetic exposure. A manuscript describing this study is now available online at *Toxicological Sciences*<sup>76</sup>.

NCTR scientists, in collaboration with CDER, extended their original studies on the pediatric anesthetics ketamine, isoflurane, and nitrous oxide to include propofol and sevoflurane. While certain concentrations of anesthesia were found to have adverse effects, scientists found that the chemical acetyl-L-carnitine provides neuroprotective properties when given prior to and during administration of the pediatric anesthetics. Validation of these findings is underway.

Another method NCTR scientists will use to assess developmental neurotoxicity is by using human neural stem-cell models and biomarkers. These data provide the scientific framework critical to updating the best practices for pediatric anesthetics.

The effects of pediatric anesthesia are also being studied in collaboration with the Mayo Clinic using an NCTR-developed method. The Mayo clinic is using NCTR-generated data to compare with some of their neuropsychological tests. Initial comparisons are showing some very significant correlations, the importance of which is under evaluation. This study will also compare the effects of childhood-administered anesthesia on brain function which may be used by FDA to establish administration guidelines in children.

Research to understand the effects of drugs on children continued in FY 2015. This research has specifically identified potential biomarkers of acetaminophen (APAP) injury in children. The pilot study compared the overdose group with healthy children and children receiving therapeutic doses of APAP. Researchers found markers in urine and blood that may be used as biomarkers (biological indicators) of liver injury. A manuscript describing the results of this study is now available online at *Toxicology and Applied Pharmacology*<sup>77</sup>.

Also in FY 2015, NCTR scientists collaborated with clinical partners at the University of Arkansas for Medical Sciences and identified several indicators associated with liver injury in children with APAP overdose compared to healthy controls. A manuscript describing these results has been accepted by *PLOS ONE*<sup>78</sup>, a peer-reviewed scientific journal.

### **Antimicrobial Resistance and the Human Microbiome**

NCTR scientists are conducting projects to limit the emergence and spread of drug resistance in bacterial pathogens. All of these projects support FDA’s regulatory needs related to the pool of antimicrobial resistance genes and bacterial pathogens in feed, foods, clinical and environmental samples, and the potential effects of transmission of resistant bacteria on human health.

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<sup>76</sup> For more information please visit <http://dx.doi.org/10.1093/toxsci/kfv150>.

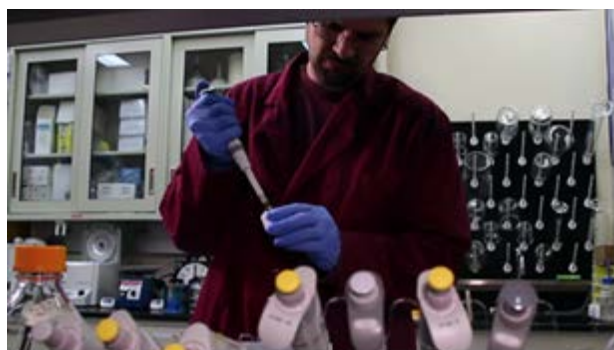
<sup>77</sup> For more information please visit <http://dx.doi.org/10.1016/j.taap.2015.02.013>.

<sup>78</sup> For more information please visit <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0131010>.

The use of veterinary antimicrobial agents in food-producing animals may result in humans being exposed continuously to low levels of antimicrobial residues in food as part of their daily diet. The human gastrointestinal tract is colonized by microorganisms – also known as the microbiome – that are known to play important roles in preventing colonization and infection by disease-causing microorganisms. Because therapeutic doses of antimicrobials shift the microbial population in the gastrointestinal tract, they may worsen the disease and promote the emergence of antimicrobial-resistant bacteria.

In FY 2015, NCTR research data was used to support the Veterinary International Conference on Harmonization Guideline 36 – [FDA Guidance #159](#)<sup>79</sup> – on the human safety of antimicrobial drugs to determine what fraction of the veterinary drug residue in the human colon remains biologically active. Going forward, scientists will determine if antimicrobial agents at food-level residue concentrations can change the antimicrobial-resistance of the human microbiome. This research will support Guideline 36, FDA, other regulatory agencies, and industry with data and methods to enhance safety evaluation of veterinary antimicrobial residues in food.

The bacteria *Clostridium perfringens* is commonly reported to cause foodborne illness in the United States. As a member of the human microbiome, this bacteria comes in contact with antimicrobial agents when a person consumes a food animal that has been treated for an infection. In FY 2015, NCTR scientists studied and determined the prevalence of antibiotic-resistance genes in *C. perfringens* and the similarity of these genes to those of other foodborne pathogens to better understand and address foodborne illness.



**NCTR scientist conducting bacterial detection analysis.**

Additionally, NCTR scientists investigated the genetic diversity and potency of the potential bioterrorism agent, *E. coli*, in FY 2015. The bacteria in the study were gathered from humans, cattle, and some food samples. More than 80 percent of the samples carried the lethal gene, and nearly 25 percent of the samples carried this gene and an additional gene that can contribute to the ability of the bacteria to attach to human intestines. The presence of these genes makes these bacteria potentially dangerous to humans if they are ingested. Furthermore, NCTR scientists found

that nearly 88 percent of these bacteria can carry antimicrobial resistance and virulence genes.

To treat and prevent human illness, NCTR is evaluating new approaches to determine the antimicrobial properties of nanoparticles towards drug-resistant pathogens to treat and prevent illnesses. Nanoparticles as antimicrobial agents offer an innovative approach to tackle antimicrobial resistance in bacteria, but their long-term effects are not known. NCTR scientists are studying the antimicrobial effects of nanoparticles on bacteria and their toxic effects in human cells. FDA needs science-based information in this area to regulate nanoparticle-containing products to ensure that they are safe for humans with no adverse health effects.

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<sup>79</sup> FDA Guidance #159 can be found at: <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052505.pdf>.

## **Improve and Safeguard Access**

NCTR conducts research to increase regulatory science capacity to evaluate FDA-regulated products in a more predictable, consistent, and efficient way. Within this Goal area, research in Bioinformatics Technologies, Precision Medicine, Nanotechnology, and Imaging Capabilities addresses the FDA Strategic Priority on Regulatory Science.

NCTR's exemplary reputation in the research community means the Center is often sought as a collaborator and advisor. NCTR partners internally and externally to share research knowledge, technical advice, and research training through global collaborations. Within this Goal area, the Global Summit on Regulatory Science, Bioinformatics Collaborations, and Nanotechnology Collaborations address the FDA Strategic Priority on Globalization.

## **Bioinformatics**

Bioinformatics is an interdisciplinary field that uses software tools to develop and improve methods for storing, managing, and analyzing large quantities of biological data. NCTR develops, provides training for, and makes available new bioinformatics tools to FDA and the global research community. With increasing amounts of data being generated by new technologies, FDA must have the software and database tools to manage the large amount of scientific data required to improve product development, safety assessments, and risk analysis. Below are some examples of NCTR's uses of bioinformatics.

### **ArrayTrack™ – FDA's Bioinformatics Infrastructure**

The foundation of NCTR's bioinformatics infrastructure is ArrayTrack™, an NCTR-developed publicly available database and data-analysis tool. NCTR staff annually trains FDA staff how to use the ArrayTrack™ functionality in research and product reviews, such as:

- SNPTrack<sup>80</sup> – stores and organizes research data and measures the impact of genetic variation on drug treatment and precision medicine
- Endocrine Disruptor Knowledge Base (EDKB)<sup>81</sup> – a database of roughly 8,000 chemicals that interfere with the endocrine systems, leading to adverse effects. This data is used to develop computer-based predictive models that are quicker and less expensive than traditional experiments.
- Estrogenic Activity Database (EADB)<sup>82</sup> – part of the EDKB discussed above; assembles data from a variety of data sources and contains 18,114 data points collected for 8,212 chemicals tested in 11 different species.

Both EDKB and EADB have been incorporated into larger government-initiated toxicological projects, such as EPA's Tox21. In FY 2015, scientists compared the EADB data with other government agencies' data and found it to be consistent, indicating EADB's value in the risk assessment of chemicals.

### **FDALabel Database – Analyzing Drug Labelings**

FDASIA requires "...inclusion of demographic subgroups in clinical trials and data analysis." NCTR scientists are refining FDALabel, an application that allows FDA to manage and analyze

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<sup>80</sup> For more information please visit: <http://www.fda.gov/ScienceResearch/BioinformaticsTools/SNPTrack/default.htm>

<sup>81</sup> For more information please visit: <http://www.fda.gov/ScienceResearch/BioinformaticsTools/EndocrineDisruptorKnowledgebase/default.htm>

<sup>82</sup> For more information please visit: <http://www.fda.gov/ScienceResearch/BioinformaticsTools/EstrogenicActivityDatabaseEADB/default.htm>

a set of more than 70,000 drug labelings. FDALabel enhances drug-safety assessments for demographic subgroups that allow for personalization of treatment in the clinical setting.

Hundreds of new or updated drug labeling with information about product indications, target populations, and adverse drug reactions are added weekly to the database. This rapid growth along with the 2006 FDA's Physician Labeling Rule, which required clear and concise prescribing information and specific formatting for drug labeling, poses a challenge for FDA staff who review labeling for safety and effectiveness data by demographic subgroups. FDALabel addresses this challenge and also makes previously-unavailable information easy for reviewers and researchers to access. FDALabel is being regularly used by:

- researchers for adverse drug-reaction studies
- FDA medical officers for drug review
- pharmaceutical companies for drug development and repositioning
- physicians and consumers for drug-safety information.

In FY 2015, NCTR updated an FDA-only version of FDALabel in collaboration with CDER to allow FDA users to look at drug-approval history, distinguish different labeling formats, search labelings by adverse reaction, and identify drugs in a specific FDA-established class.

### **Precision Medicine**

Biomarker development is a tool for predicting FDA-regulated product toxicity and providing precision medicine solutions. A biomarker is a biological indicator of a biological state or condition. NCTR scientists continue research to identify new biomarkers that can be used to identify populations susceptible to drug side-effects, predict harmful effects of drugs during safety evaluations, reduce, or reverse cardiac injury, or improve therapeutic patient treatments as shown in the following research.

Side-effects of drugs based on sex-differences may not be adequately addressed in preclinical evaluations and better methods are needed to identify susceptible populations. In FY 2015, NCTR scientists assembled a comprehensive list of drug-interacting enzymes – biological accelerators – and linked them to specific genetic interactions. Twenty nine of these enzymes were found to be different based on gender and involved in the metabolism of more than 600 drugs. The successful construction of this database will allow the modeling and prediction of possible toxicity based on sex differences.

Chronic cardiotoxicity – toxicity of the heart – induced by an anticancer drug, doxorubicin (DOX), is dose-dependent, cumulative, irreversible, and seemingly more prevalent in men. It is also a major concern of clinical oncologists. However, the mechanisms that cause the difference in susceptibility between the sexes are unclear. In FY 2015, NCTR scientists developed a mouse model of sex-related differences in DOX cardiotoxicity. The observation was that male mice did show a greater susceptibility to DOX than female mice. This newly established mouse model will help to assess sex-related differences and improve safety assessments.

Also to help address DOX cardiotoxicity, NCTR scientists partnered with the National Cancer Institute, Korea University, and the Arkansas Heart Hospital. This collaboration used a mouse model of DOX-induced heart injury to develop candidates for early biomarkers of cardiotoxicity. Currently, the dose amount of this cancer-fighting drug is determined by general estimates of toxicity. This study identified a dosage likely to lead to cardiac disease and also suggests identification signals – combination of cell death, thickening and scarring of tissue, and the



formation of a small cavity in a cell – that may contribute to the development of cardiac impairment due to DOX-treatment. These early biomarkers of DOX-induced heart injury will produce more effective treatment regimens. A paper describing this study is available online at *Toxicology and Applied Pharmacology*.<sup>83</sup>

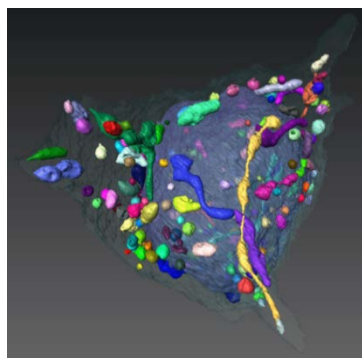
Another precision medicine effort completed in FY 2015 identified genetic variants associated with cardiovascular disease and responses to anti platelet-aggregation drugs – drugs that decrease the clumping together of platelets in the blood which may form a clot. NCTR scientists performed association studies among 120 Amish participants. Eight genetic variants in the Amish population were validated as being associated with adverse reactions to an anti-platelet aggregation drug. Studies for a genetic variant showing an association with increased aspirin efficacy towards anti-platelet aggregation are ongoing.

Also ongoing is NCTR research looking at autism spectrum disorders that are on the rise and of which the exact cause is unknown. It has been proposed that stressors occurring in the uterus make offspring more vulnerable to mood disorders, although the transmission between parent and offspring is not well-understood. NCTR scientists, in collaboration with UAMS, are conducting a study to identify new biomarkers for risk assessment of autism spectrum disorders during pregnancy. Once the biomarkers are validated in a larger study population, it may be possible to develop potential drug interventions that may enhance a positive outcome in offspring.

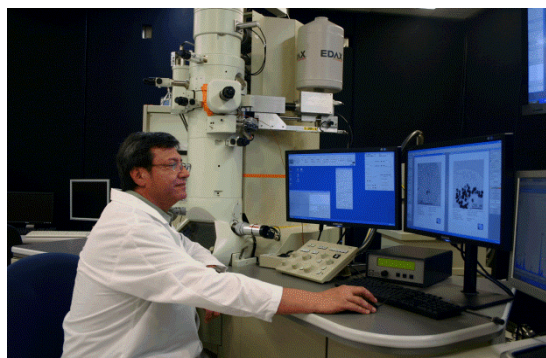
### **Nanotechnology**

The NCTR and ORA Nanotechnology Core Facility (NanoCore) is supporting collaborative efforts within FDA, other U.S. government agencies, and university researchers providing analytical project support. This work will inform FDA and other government agencies on the toxicity and safety of nanotechnology-based materials.

FDA reviews submissions for new and generic drugs, medical devices, food, and veterinary products based on consensus standards developed in collaboration with industry. There has been a global increase of nanotechnology research and maturity of nanotechnology-enabled products regulated by FDA. The NanoCore conducts regulatory science in Nanotechnology to foster



**This NanoCore image shows a 3D reconstruction of a rat neuron, an example of the two- and three-dimensional electron microscopy techniques to quantify mitochondria defects.**



**NanoCore scientist conducting electron microscopy.**

<sup>83</sup> For more information please visit <http://dx.doi.org/10.1016/j.taap.2014.10.006>

development of FDA-regulated products containing nanomaterials and the standards to assess the safety of these products.

The NCTR NanoCore, along with CDER and CVM, is conducting collaborative studies to understand how these tiny nanoparticles travel through the blood and distribute in different parts of the human body. FDA scientists are using an advanced modeling approach, called Physiologically-Based Pharmacokinetic (PBPK) modeling to quantitatively describe and predict the biodistribution of both the nanoparticles and drug molecules. Results from these studies will help to establish science-based minimum standards for conducting hazard analysis of regulated products containing nanoparticles.

### **Magnetic Resonance Imaging (MRI)**

Full-brain MRI imaging offers the potential to dramatically improve detection of neurotoxicity produced by new drugs and facilitate new drug development and evaluations. Additionally, NCTR has made significant progress towards the development of minimally invasive diagnostic methods for identifying nervous-system tissue anomalies. The technology, derived from FDA-regulated MRI instruments, is called magnetic resonance spectroscopy (MRS). NCTR in collaboration with Huntington Medical Research Institute has developed a method to improve the use of MRS scans to predict or diagnose medical abnormalities without the need for biopsies. Scientists are currently using this NCTR-developed method for identifying Alzheimer's, dementia, and mild cognitive impairment and soon will begin a project to identify traumatic brain injury.



**Preclinical MRI machine - one of the pieces of equipment used in the NCTR Bio-Imaging Facility.**

In FY 2015, NCTR researchers in collaboration with CDER used ten neurotoxicants to test the ability of MRI technology to both detect and follow the course of events typically observed under traditional evaluation. It was found that the MRI can provide the equivalent of 64 visual “slices” of the brain instantly to the pathologist for targeting regions of interest for further evaluations.<sup>84</sup>

New and continuing imaging research at NCTR includes:

- studying the relationship of MRI findings with biological fluid biomarkers
- using an advanced sodium MRI approach to detect very early signals of neurotoxicity
- using MRI approaches to detect liver-transport function as a marker of drug-induced liver injury.

### **Collaborations**

A critical component of NCTR's and FDA's science portfolio is collaborations with other entities to leverage knowledge and to establish research partnerships where expertise from each entity can contribute to regulatory-science research projects. A strong in-house science base and

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<sup>84</sup> For additional information, the manuscript is available online at Regulatory Toxicology and Pharmacology. <http://www.sciencedirect.com/science/article/pii/S0273230014002153>

a network of collaborations is necessary to help support FDA's success in addressing public-health challenges.

Scientific advancements are enhanced by participation in meetings and conferences where experts present their most current research and through collaborations and relationships, both formal and informal, that provide FDA with access to cutting-edge science. Support of this important strategic priority is reflected in the following highlighted collaborations.

### **Global Summit on Regulatory Science**

Because of the importance for international regulators, policy makers, and scientists to exchange views on how to develop, apply, and implement innovative methodologies into regulatory assessments, NCTR established an annual Global Summit on Regulatory Science (GSRS).

Now in its sixth year, GSRS' goal is to engage the global community and harmonize research strategies via collaborations that aim to build knowledge of and promote regulatory science, define research needs, and seek to strengthen product safety worldwide by training regulatory scientists. The GSRS is led by the Global Coalition which is comprised of regulatory science leaders from around the world. NCTR's Director serves as the FDA scientific representative and co-chair of the Coalition's executive committee and works with the Coalition to promote global interaction.

The 2015 Global Summit was hosted by the European Food Safety Authority in Parma, Italy and included more than 100 leading international scientists from 25 countries. A paper titled "Genomics in the Land of Regulatory Science" was published in FY 2015 in *Regulatory Toxicology and Pharmacology*<sup>85</sup> that summarized the 2014 Global Summit.

### **Bioinformatics Collaborations**

NCTR and the Arkansas state university system held the first annual Arkansas Bioinformatics Consortium<sup>86</sup> conference in March 2015 to leverage statewide bioinformatics capabilities. The conference was organized by NCTR and the Arkansas Research Alliance. The topics this year focused on precision medicine and regulatory sciences applications. The second annual meeting is scheduled for April 2016.

This consortium will increase resources for FDA regulatory science and strengthen the FDA Memorandum of Understanding (MOU) with the state of Arkansas.

### **Nanotechnology Collaborations**

The NCTR and ORA Nanotechnology Core Facility (NanoCore) is supporting collaborative efforts within FDA, other U.S. government agencies, and university researchers providing analytical project support. NCTR and the NanoCore are currently providing analytical support for nanotechnology investigative projects with FDA Product Centers CDRH, CDER, CFSAN, CVM, and ORA. This work will inform FDA and other U.S. government agencies on the toxicity and safety of nanotechnology-based materials.

Through an MOU between the State of Arkansas and FDA, a consortium of five Arkansas research universities provided FDA with comprehensive data on the synthesis and detection of graphene. In FY 2015, the NanoCore identified that graphene was contaminated with endotoxin – cell wall debris from bacteria – which can lead to a false determination that graphene is toxic.

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<sup>85</sup> For more information <http://www.sciencedirect.com/science/article/pii/S0273230015000550>

<sup>86</sup> For more information <http://www.arkansasbioinformatics.org>



The NanoCore has taken procedures to reduce the endotoxin to acceptable levels so that graphene can be used in toxicological studies. This information is important because of the human exposure to graphene-based nanomaterials rapidly being developed for use in a variety of biomedical and food-packaging applications, and which is being touted in scientific literature as a platform for drug delivery. NCTR continues to coordinate, conduct, and collaborate with researchers around the globe to meet FDA regulatory-research requirements.

### **FUNDING HISTORY**

<b>Fiscal Year</b>	<b>Program Level</b>	<b>Budget Authority</b>	<b>User Fees</b>
<b>FY 2013 Actual</b>	\$54,965,000	\$54,965,000	\$0
<b>FY 2014 Actual</b>	\$62,488,000	\$62,488,000	\$0
<b>FY 2015 Actual</b>	\$63,312,000	\$63,312,000	\$0
<b>FY 2016 Enacted</b>	\$63,331,000	\$63,331,000	\$0
<b>FY 2017 President's Budget</b>	\$60,277,000	\$60,277,000	\$0

### **BUDGET REQUEST**

The FY 2017 Budget Request is \$60,277,000 which is all budget authority. The budget authority decreases by \$3,054,000 compared to the FY 2016 Enacted level. This reduction in budget authority will delay the progress or start of critical research projects at NCTR on food safety issues, delaying advances in regulatory science.

The FY 2017 budget request allows NCTR to conduct ground-breaking research to support the FDA Strategic Goals of Oversight and Improve and Safeguard Access. These areas of research include emerging technologies, such as nanotechnology, bio-imaging, bioinformatics, and biostatistics. Specifically, NCTR will continue to:

- expedite the translation of scientific advancements to regulatory application
- develop new tools and approaches to assess the safety and efficacy of regulated products
- integrate toxicology safety assessments maximizing existing and emerging technologies
- provide valuable research data on products using new technologies
- help FDA better understand data submissions that are generated using new technologies.

NCTR will conduct research to enhance oversight of FDA-regulated products by using funding to develop tools and methods that will be used to inform standards development, analysis, and decision-making for the safety of FDA-regulated products and to expedite the translation of basic science to regulatory application. This research allows FDA to capitalize on the global scientific advancements and expand FDA's regulatory-science capacity by increasing the speed at which *in vitro* and animal models are put to use in determining safety of FDA-regulated products.

NCTR will conduct research to improve and safeguard access to FDA-regulated products by increasing regulatory-science capacity to evaluate FDA-regulated products in a more predictable, consistent, and efficient way. NCTR will use base funding to conduct research to advance bioinformatics technologies, precision medicine, biomarkers, bio-imaging, and nanotechnology. This research will be done in collaboration with scientists from around the world in government,

academia, and industry to exchange views on how to develop, apply, and implement innovative methodologies into regulatory assessments.

**BUDGET AUTHORITY**

**Food Safety: \$7.2 million (-\$3.054 million)**

Center: -\$3.054 million

As part of the FY 2017 Budget, NCTR will delay advances in science needed for regulatory decisions and scale back investment in new research areas critical to public health.

Business and academia are moving rapidly to take advantage of new technology and scientific understanding, and FDA must keep pace to fulfill its mission to protect the public. Without maintaining a level budget for research, FDA’s ability to translate the science required for regulatory decision-making will be slowed in select areas.

**PERFORMANCE**

NCTR’s performance measures focus on research to advance the safety of FDA-regulated products, on developing a strong FDA science base for emerging technologies, and on providing personalized medicine solutions in order to protect and improve the health of the American public as detailed in the following table.

Measure	Most Recent Result / Target for Recent Result	FY 2016 Target	FY 2017 Target
<p><u>263103</u>: Conduct translational and regulatory research to advance the safety of products that FDA regulates (<i>Output</i>)</p>	<p>FY15: Research demonstrated that silver nanoparticles can reach the bone marrow and liver, and result in cellular toxicity when using an animal model(<i>Target Met</i>)</p> <p>FY15: Expression levels of 61 genes were significantly altered in heart mitochondria before the occurrence of heart damage, suggesting these genes could be used as early biomarkers of cardiotoxicity (<i>Target Met</i>)</p>	<p>Experimental data generated to demonstrate the advantages and benefits of new in vitro method to rapidly and accurately detect cellular toxicity</p>	<p>1) Finalize research to validate a minimally invasive 3-dimensional MRI technique to more accurately evaluate brain neurotoxicity</p> <p>2) Report preliminary findings on the neurological effects of commonly used chemotherapy drugs doxorubicin and cyclophosphamide</p>
<p><u>263201</u>: Develop science base for supporting FDA regulatory review of new and emerging technologies (<i>Output</i>)</p>	<p>FY15: Paper published outlining the benefits of in vitro approaches (e.g. neural stem cells) in combination with imaging approaches (e.g. calcium imaging) (<i>Target Met</i>)</p>	<p>Provide data that can inform FDA's regulatory need concerning sevoflurane and propofol use in children</p>	<p>1) Provide data on the toxicity of graphene nanomaterials leading to guidance for FDA-regulation of nanomaterials</p> <p>2) Identify and validate predictive biomarkers for nanomaterial-associated immunotoxicity</p>

Measure	Most Recent Result / Target for Recent Result	FY 2016 Target	FY 2017 Target
<u>262401</u> : Develop biomarkers to assist in characterizing an individual's genetic profile in order to minimize adverse events and maximize therapeutic care ( <i>Output</i> )	FY15: Research generated a mutational profile of Triple Negative Breast cancer to aid in personalized medicine approaches to treat breast cancer ( <i>Target Met</i> )  FY15: Initial evaluation of biomarkers completed via Nuclear Magnetic Resonance ( <i>Target Met</i> )	Identify potentially predictable drug/drug receptor combinations that can cause rare and unpredictable side effects	Complete initial phase of research to Identify drugs that have differential toxicological effects depending on age and/or sex of an individual in an effort to develop a bioinformatics-based safety assessment
<u>264101</u> : Develop risk assessment methods and build biological dose-response models in support of food protection ( <i>Output</i> )	FY15: Researchers identified emerging strains of E. coli that can cause foodborne outbreaks in humans and could potentially be used as agents in a bioterrorism event ( <i>Target Met</i> )	Data analysis completed on study to enhance immunity to norovirus-like particle vaccine	Develop bioinformatics methods in support of microbial pathogen characterization and food protection
<u>263104</u> : Use new omics technologies to develop approaches that assess risk and assure the safety of products that FDA regulates ( <i>Output</i> )	FY15: A potential biomarker of impending neuronal damage has been discovered when using an animal model( <i>Target Met</i> )	Utilize new omics technologies to provide translational insight into prevention and prognosis of drug induced liver injury	Finalize research to identify translational biomarkers to aid in prevention and/or early detection of Drug Induced Liver Injury induced by FDA-regulated products
<u>263102</u> : Develop computer-based models and infrastructure to predict the health risk of biologically active products ( <i>Output</i> )	FY15: Developed a strategy for potentially identifying drug-repurposing candidates for Cystic Fibrosis patients using a bioinformatics approach ( <i>Target Met</i> )	Statistical and data mining techniques identified for use in application to cancer therapeutics	Develop and refine FDA Label with new functionality based on feedback from FDA reviewers and scientists

The following selected items highlight notable results and trends detailed in the performance table.

- research to advance the safety of FDA-regulated products
- strong FDA science-base for emerging technologies
- precision medicine solutions

### **Advance the Safety of FDA-Regulated Products**

NCTR scientists have extended their original findings on the pediatric anesthetics ketamine, isoflurane, and nitrous oxide to include propofol and sevoflurane. Initial research indicated that certain concentrations of propofol had adverse effects.

However, scientists also found that administration of the drug, acetyl-L-carnitine, provides some protection to the nervous system when given prior to and during administration of anesthetics. In FY 2015, a paper outlining the benefits of in vitro approaches (e.g. neural stem cells) in combination with imaging approaches (e.g. calcium imaging) was published. In FY 2016,

scientists at NCTR will research new *in vitro* methods to rapidly and accurately detect damage to cells that is caused by exposure to FDA-regulated products.

### **Develop Science Base for New and Emerging Technologies**

Results from studies exploring miRNA (unique genetic markers found in higher-level organisms) responses in humans with liver injury, suggest that miRNAs might provide needed information to industry and to clinicians managing patients who experience drug-induced injury. In FY 2015, scientists developed a strategy for potentially identifying drug-repurposing candidates for Cystic Fibrosis patients using a bioinformatics approach. In FY 2016, NCTR scientists will provide data to address FDA inquiries regarding use of the anesthetics sevoflurane and propofol in children.

### **Personalized Medicine**

Investigators determined that sex differences, and ethnicity and age influenced gene-expression levels in normal kidney tissue. Investigators also identified genetic variations that increase the risk of adverse reactions to carbamazepine, a drug used to treat epilepsy. Preliminary results revealed that two genetic markers, in particular, are highly associated with adverse drug reactions. In FY 2015, researchers generated a mutational profile of Triple Negative Breast cancer to aide in personalized medicine approaches to treat breast cancer. In FY 2016, NCTR will perform research to identify combinations of drugs and drug receptors (any part of a cell with which a drug interacts to trigger a response or effect) that may lead to adverse patient side effects.

## **PROGRAM ACTIVITY DATA**

### **National Center for Toxicological Research Program Activity Data (PAD)**

<b>Program Workload and Outputs</b>	<b>FY 2015 Actual</b>	<b>FY 2016 Estimate</b>	<b>FY 2017 Estimate</b>
<b>Research Outputs</b>			
Research Publications	141	150	155
Research Presentations	160	148	148
Patents (Industry)	5	5	5
<b>Leveraged Research</b>			
Federal Agencies (Interagency Agreements)	3	3	3
Nongovernmental Organizations	19	19	19
<b>Active Research Projects</b>	180	165	155