NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

(Dollars in Thousands)	FY 2016 Final	FY 2016 Actuals	FY 2017 Annualized CR	FY 2018 President's Budget	FY 2018 President's Budget +/- FY 2017 CR
National Center for Toxicological Research (BA Only).....	63,331	63,329	63,211	60,211	-3,000
FTE.....	299	299	304	304	---

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 support FDA's strategic priorities to advance regulatory science and engage globally to encourage the implementation of science-based standards. Further, in support of FDA's strategic goals to Enhance Oversight 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 and understand the risks and benefits of nanomaterials used in FDA-regulated products
- provide strategies to reduce and rapidly detect contaminants in FDA-regulated products
- use biomarkers ─ biological indicators of disease ─ to foster precision medicine
- accelerate FDA's capability to manage and analyze research data using bioinformatics
- reduce costly and dangerous surgeries by expanding minimally-invasive imaging capabilities
- expedite the translation of laboratory findings to the clinic and to regulatory application.

The following selected accomplishments[60] demonstrate NCTR's delivery of its regulatory science and public-health responsibilities within the context of current priorities[61].

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 Enhancing Oversight, NCTR conducts research focused on Pediatric Medicine, Cancer, Biomarker Development, and Antimicrobial Resistance that also address the FDA Strategic Priority on Regulatory Science.

[60] More information on NCTR Research Accomplishments can be found at: http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/ResearchAccomplishmentsPlans/default.htm.
[61] Please visit www.fda.gov for additional program information and detailed news items.

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 potentially adverse 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. 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.

NCTR scientists, collaborating with CDER, found that longer durations of exposure to the pediatric anesthetics ketamine, isoflurane, nitrous oxide, propofol, and sevoflurane had adverse effects. Additionally, the scientists found that the chemical acetyl-L-carnitine provides neuroprotective or therapeutic properties when given before and during administration of the pediatric anesthetics. Information about this study can be viewed in the May 2016 issue of *Anesthesiology*.[62]

FY 2016 data from an NCTR study also show that prolonged exposure to anesthetics, such as sevoflurane, is capable of inducing and maintaining an effective surgical level of anesthesia in the developing nonhuman primate. Prolonged exposure also resulted in profound genetic changes, cytokine ─ molecules that aid in immune response ─ levels, breakdown of fats, and subsequently, nerve-cell damage. These data show that anesthetic-induced damage was also associated with changes in fat content. Therefore, theoretically fat content could be used as a biomarker for damage. In general, these data provide the scientific framework critical to updating the best practices for minimally-invasive pediatric anesthetic-assessment methods.

The effects of pediatric anesthesia are also being studied in collaboration with colleagues at the Mayo Clinic using an NCTR-developed method for assessing brain function in children. This method has been used extensively in nonhuman primate studies conducted at NCTR. The Mayo study plans to finish study subject enrollment in early FY17, after which data analyses and interpretation will begin. This study aims to determine if there are significant adverse effects of general anesthesia on subsequent brain function when given in the important period of rapid brain development after birth. This information may inform agency decisions about labeling and/or best practices for pediatric general anesthesia.

Research to understand the effects of drugs on children continued that 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 biological indicators, also called biomarkers, of liver injury. A manuscript written in FY 2016 verifies hemeoxygenase 1 (HMOX1) as a biomarker of APAP liver injury in blood plasma and can be found in *Proteomics Clinical Application*.[63] Additional research analyzing urine and blood is now being completed in adults who suffered acute liver failure and will continue through FY 2017. Identifying liver-injury biomarkers are critical to improving the delivery of precision medicine by allowing for earlier and targeted treatment in children and adults.

[62] For more information visit: https://www.researchgate.net/publication/303180769_In_Vivo_Monitoring_of_Sevoflurane-induced_Adverse_Effects_in_Neonatal_Nonhuman_Primates_Using_Small-animal_Positron_Emission_Tomography.
[63] For more information visit: http://onlinelibrary.wiley.com/doi/10.1002/prca.201600123/epdf.

Rapid Detection of Bacterial Contamination in Foods

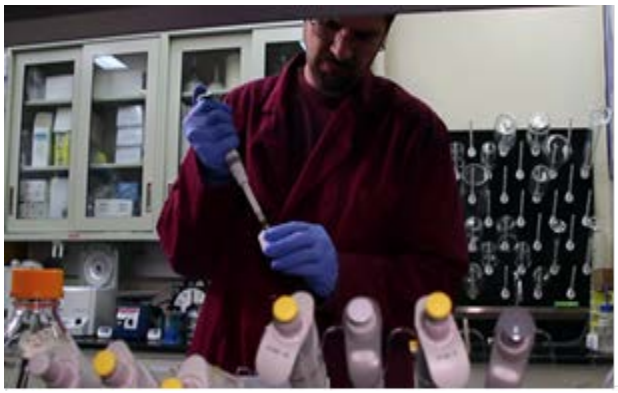
In FY 2016, NCTR scientists developed a method for rapidly detecting low levels of harmful bacteria such as *E-coli* O157:H7 and *Shigella* in foods. This method measures single bacterial cells without requiring a time-consuming period of growth on a Petri dish. Information about this research may be found online at the *International Journal of Food Microbiology*[64].

In FY 2017, collaborative research efforts by NCTR and CFSAN scientists include looking for ways to detect:

- Listeria monocytogenes faster,
- lower numbers of the *Listeria* cells in foods, and
- test large numbers of samples as to the likelihood that they came from a particular source.

Antimicrobial Resistance

CDC estimates that each year roughly one in six Americans get sick from eating contaminated food. NCTR scientists continue to conduct projects to limit the emergence and spread of drug resistance in bacterial pathogens that compromise our ability to treat foodborne illnesses. 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.



NCTR scientist conducting bacterial detection analysis.

In FY 2016, NCTR scientists used techniques to better understand the diversity of the organisms and studied the presence of plasmids ─ independent DNA molecules commonly found in cells ─ that can contribute to antimicrobial resistance and enhanced disease-causing ability. Understanding what contributes to antimicrobial resistance in these organisms will help develop ways to better address foodborne illness.

Also in FY 2016, NCTR scientists compared the relative impact of antimicrobial exposure on the dissemination of plasmids that can transfer antimicrobial resistance to a cell. This vastly understudied area of research evaluated the transfer of resistance in *Salmonella enterica* strains exposed to different concentrations of commonly used antimicrobial drugs. A manuscript describing this research can be found at *Genome Announcements*[65].

NCTR scientists are investigating other emerging public health concerns such as the genetic diversity of shiga-toxin producing *Escherichia coli* (STEC). The bacteria in the study were gathered from humans, cattle, and some food samples. In FY 2016, scientists completed detailed analyses that show these bacteria fall into distinct groupings based on their gene profiles. These data may help FDA to better understand which genetic factors influence the ability of STEC to persist in the food supply and potentially cause human disease.

[64] For more information visit: http://www.sciencedirect.com/science/article/pii/S0168160515300970.
[65] For more information visit: http://genomea.asm.org/content/4/5/e01122-16.abstract.

Cell Mutations for Prediction

Genes are found in the DNA of every human cell and control how the cell functions ─ including how quickly it grows, how often it divides, and how long it lives. Despite all that is known about genes and their relationship to disease, more research is needed to better understand how genetic changes affect cells and disease, such as cancer. This knowledge may lead to improvements in the ability to develop personalized treatment plans.

In FY 2016, NCTR researchers used new technology (MARDI) – Mutation Analysis with Random DNA Identifiers– called DNA tagging that applies identification markers to DNA to improve detection of mutation not observed by existing methods. This less expensive technique identifies mutations faster and more accurately. Therefore, it can confirm mutations and exclude false positives – two critical aspects for drug evaluation. A manuscript describing the results is available online at *Environmental and Molecular Mutagenesis*[66].

Also in FY 2016, NCTR scientists identified unique rat and human microRNAs capable of discerning drug-induced fatty liver from non-alcoholic fatty liver disease (NAFLD), one of the most common reasons for liver transplants. This identification may allow for early detection, monitoring of disease progression, and improved drug selection in preclinical development programs. A manuscript reporting the study is available online at *Scientific Reports*[67].

In FY 2016, NCTR in collaboration with the National Taiwan University developed new algorithms to improve classification of liver disease patients into two subgroups ─ treatment sensitive and treatment non-sensitive patients ─ and an accompanying method to evaluate treatment effectiveness in each subgroup. This new procedure effectively identifies how a subgroup would respond so that a treatment, such as a cancer treatment, can be approved and administered only to those patients who are likely to benefit ─ improving precision medicine. A manuscript describing this study can be found at *BMC Medical Research Methodology*[68].

Improve and Safeguard Access

NCTR conducts research to evaluate FDA-regulated products in a more predictable, consistent, and efficient way and is often sought out as a collaborator and advisor due to its exemplary reputation in the research community. Within this Goal area, research in Bioinformatics, Precision Medicine, Nanotechnology, and Bio-Imaging addresses the FDA Strategic Priority on Regulatory Science. The Global Summit on Regulatory Science, Bioinformatics Collaborations, and Nanotechnology Collaborations address the FDA Strategic Priority on Globalization.

Bioinformatics Technologies and Resources

Bioinformatics 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 bioinformatics tools to FDA and the global research community. FDA must have the software and database tools to manage the large amount of scientific data generated by new technologies required to improve product development, safety assessments, and risk analysis. Below are examples of NCTR's bioinformatics program.

[66] For more information visit: http://onlinelibrary.wiley.com/doi/10.1002/em.21992/abstract;jsessionid=97C51EA272D3BC16468426299C358AB0.f02t03
[67] For more information visit: http://www.nature.com/articles/srep23709
[68] For more information visit: http://www.ncbi.nlm.nih.gov/pubmed/26646831

Publically Available Dataset/Database Name	Description
DILIrank	Dataset listing 1,036 FDA-approved drugs ranked by potential to cause drug-induced liver injury (DILI); the largest publically available annotated DILI dataset. The 1,036 drugs listed were defined and verified as shown below: • 192 "Most-DILI" concern • 278 "Less-DILI" concern • 312 "No-DILI" concern • 254 "Ambiguous-DILI" concern DILIrank may be used by FDA reviewers, industry for drug development, and researchers for adverse drug reaction studies. It can be used to build scientific models that predict the likelihood of a drug to cause liver injury. A manuscript describing this study can be found online at *Drug Discovery Today*[69].
Endocrine Disruptor Knowledge Base (EDKB)[70]	Database of roughly 3,000 chemicals that interfere with the endocrine system; used to develop computer-based predictive models that are quicker and less expensive than traditional experiments. Incorporated into larger government-initiated toxicological projects, such as EPA's Tox21.
Estrogenic Activity Database (EADB)[71]	Part of EDKB that assembles data from a variety of data sources and contains 18,114 data points collected for 8,212 chemicals tested in 11 different species. Incorporated into larger government-initiated toxicological projects, such as EPA's Tox21.

[69] For more information visit: http://www.sciencedirect.com/science/article/pii/S1359644616300411
[70] For more information visit: http://www.fda.gov/ScienceResearch/BioinformaticsTools/EndocrineDisruptorKnowledgebase/default.htm
[71] For more information visit: http://www.fda.gov/ScienceResearch/BioinformaticsTools/EstrogenicActivityDatabaseEADB/default.htm

FDALabel Database – Drug Labelings[72]	Hundreds of new or updated drug labels with information about product indications, target populations, and adverse drug reactions are added weekly. FDALabel makes previously unavailable information easy for researchers and FDA staff who review labelings for the safety and effectiveness of drugs to access. FDALabel is 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 2016, NCTR customized FDALabel for use by CDER and CBER reviewers to perform customizable searches of about 90,000 labeling documents.

Text Mining

NCTR, in collaboration with National Institutes of Health, applied a text-mining method to integrate two different types of research data resulting in identification of meaningful data associations. Text-mining methods apply computation approaches onto text for word recognition, frequency of use, and association – identifying similarities between documents based on such aspects as the words used. A simple example of text mining is the filtering or identification of e-mail messages containing certain words.

The NCTR study demonstrated that text-mining methodologies is an effective approach to integrate diverse data sources from different technologies. This allows FDA and the research community to better understand the mechanisms of disease and toxicity. A manuscript published in FY 2016 detailing the study is available online at *Toxicological Sciences*[73].

Precision Medicine

Biomarker development is a method for predicting FDA-regulated product toxicity and providing precision medicine solutions such as individually-tailored therapeutic drug regimens. 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
- improve therapeutic patient treatments as shown in the following research.

In FY 2016, NCTR scientists, with researchers from Beijing Pediatric Research Institute and the Arkansas Department of Health, determined that the levels of a key enzyme are controlled by microRNAs – small nucleic acids. This enzyme is involved in the metabolism of 6-10 percent of drugs in current clinical use. It is already known that an individual's genetics affect the

[72] For more information visit: http://www.fda.gov/ScienceResearch/BioinformaticsTools/ucm289739.htm
[73] For more information visit: http://toxsci.oxfordjournals.org/content/150/1/64

activity of this enzyme, which can change the effectiveness and toxicity of certain drugs. However, the researchers identified a specific microRNA that suppresses this enzyme activity, bringing up new questions about the genetic and environmental factors that may affect drug metabolism. A manuscript describing this study is available online at *Biochemical Pharmacology*[74].

Doxorubicin (DOX) is an effective chemotherapy treatment that is limited by its chronic cardiotoxicity ─ toxicity of the heart ─ which is dose-dependent, cumulative, and irreversible. Because early biomarkers of drug-induced cardiotoxicity could enable a precision medicine-based approach to chemotherapy treatment, NCTR scientists are actively researching DOX.

In FY 2016, scientists from NCTR, National Cancer Institute, Korea University, and UltraPath Imaging identified a panel of 61 genes from DOX-treated mice that may be early indicators of drug cardiotoxicity. These genes were expressed differentially in heart mitochondria before and after drug-induced cardiac injury. Researchers found that a high dose of the heart-protecting drug dexrazoxane significantly reduced genetic changes and eliminated evidence of cardiac disease. Information about the study is available at *Toxicology and Applied Pharmacology*[75].

In another DOX study, NCTR scientists measured significant early changes in the levels of multiple metabolites ─ products of metabolism ─ in blood and heart tissue from mice treated with DOX. Early metabolic changes observed in plasma during the initial stages of DOX-induced cardiac injury could indicate biomarkers of cardiotoxicity. A manuscript describing the study is now available at *Journal of Applied Toxicology.*[76]

Also within precision medicine, researchers at NCTR and CDER, Wright Patterson Air Force Base, Wright State University, and CDC constructed a model to predict adverse outcomes from exposure to thyroid-acting chemicals, drugs, radioactive materials, or iodine deficiency. This model takes into account the lactating mother and the rapid-developing endocrine system of the nursing infant from delivery to 90 days postpartum. This model may help to establish national and international guidelines for breast milk iodine concentrations, an important area with little existing data. Information about the study is available online at *PLOS One*[77].

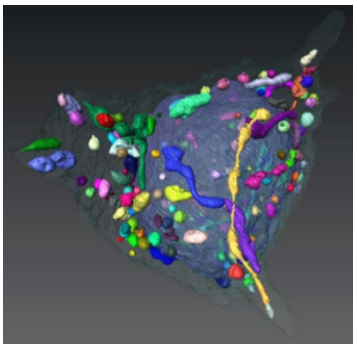
Nanotechnology

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

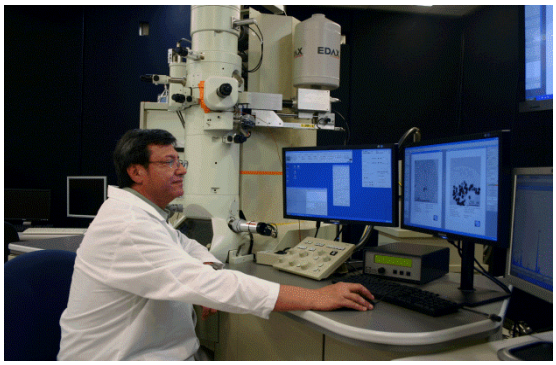
There has been a global increase of nanotechnology-enabled products regulated by FDA. The NanoCore conducts research to foster development of FDA-regulated products containing nanoparticles and the standards to assess the safety of these products. The NanoCore is conducting collaborative studies with CDER and CVM to understand how nanomaterials travel through the blood and distribute in different parts of the body.

[74] For more information visit: http://www.sciencedirect.com/science/article/pii/S0006295215005390
[75] For more information visit: http://www.sciencedirect.com/science/article/pii/S0041008X16300266
[76] For more information visit: http://onlinelibrary.wiley.com/doi/10.1002/jat.3307/abstract
[77] For more information visit: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0149300

In one FY 2016 project, NCTR scientists initiated research involving nanocrystals and their interaction with intestinal microbiota. Nanocrystals are promising drug molecules that increase a drug's solubility, in turn increasing the effectiveness of that drug. Results from these studies will help to establish science-based minimum standards for conducting hazard analysis of regulated products containing nanomaterials.



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.

The biological impacts of nanomaterials are virtually unknown, especially if the material has the potential to be migrated to food and ingested. In collaboration with the Arkansas Research Alliance[78], NCTR developed a model to test the effects of graphene on intestinal microbiota living in the human gut, also called the human microbiome. The study, which continues in FY 2017, is evaluating graphene-induced toxicity to the intestinal microbiota and the gut-associated immune response. Early results suggest no major effects to growth of gut bacteria belonging to human microbiome and no major effects to intestinal permeability. Having access to science-based information like this is critical for FDA to regulate nanomaterial-containing products to ensure that they are safe for humans.

Magnetic Resonance Imaging (MRI)

Full-brain MRI imaging offers the potential to dramatically improve detection of neurotoxicity produced by new drugs, and to spur new drug development and evaluations. Additionally, NCTR continues 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. The method is being used to identify Alzheimer's, dementia, and mild cognitive impairment.

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

[78] For more information visit: http://www.aralliance.org/.

In FY 2016, NCTR developed a method using MRI and image analysis of MRI files to screen brain samples for evidence of neuro-irregularities (presumed toxicities). The method could potentially qualify brain-toxicity biomarkers while also locating the effected tissue within the brain. The method has been to monitor and assess hexachlorophene, a potent neurotoxicant used to treat burns and prevent *Staphylococcus aureus* infections in infants. A publication about this method can be found in *Neurotoxicology*[79].

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 early signals of neurotoxicity
- correlating MRI results to current assessment methods to assess MRI sensitivity.

Collaborations

A critical component of NCTR's and FDA's science portfolio is collaborations with other entities to leverage knowledge and to establish partnerships where expertise from each entity can contribute to regulatory-science research projects. A strong in-house science base and a network of collaborations are necessary to support FDA's success in addressing public-health challenges.

Scientific advancements are enhanced by participation in meetings and conferences where experts present their current research. Collaborations and relationships built at these meetings provide FDA with access to cutting-edge science. Support of this important strategic priority is reflected in the following highlighted collaborations. Below are some of those important collaborations.

Global Summit on Regulatory Science

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

Now in its seventh year, the Global Summit's 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 Global Summit is led by the Global Coalition which is comprised of regulatory science leaders from around the world. NCTR's Director serves as the co-chair of the Coalition's executive committee and works with the Coalition to promote global interaction. The 2016 Global Summit provided a forum for scientists from government, industry, and academia from 19 countries. The 2017 Global Summit on Regulatory Science is planned to be held in Brasilia, Brazil on September 18-22, 2017.

Bioinformatics Collaborations

NCTR and the Arkansas state university system held the second annual Arkansas Bioinformatics Consortium[80] conference in April 2016 to leverage statewide bioinformatics capabilities. The conference – organized by NCTR and the Arkansas Research Alliance – focused on precision medicine and regulatory sciences applications.

[79] For more information visit: http://www.sciencedirect.com/science/article/pii/S0161813X16301516
[80] For more information visit: http:// www.arkansasbioinformatics.org

In September 2016, in support of the Precision Medicine Initiative, the NCTR-led 1st Sequencing Quality Control Phase 2 public workshop was held at the NIH campus with over 150 participants and 20 presentations given. The workshop resulted in the establishment of a working group to tackle projects to assess the technical performance of next-generation sequencing technologies for precision medicine.

Nanotechnology Collaborations

The NCTR/Office of Regulatory Affairs Nanotechnology Core Facility (NanoCore) supports collaborative efforts within FDA, other U.S. government agencies, and with university researchers providing analytical project support. NCTR and the NanoCore provide analytical support for nanotechnology investigative projects with FDA Product Centers CDRH, CDER, CFSAN, CVM, and ORA. This work informs FDA and other U.S. government agencies on the toxicity and safety of nanotechnology-based materials.

Through a Memorandum of Understanding 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. This study of graphene continues into FY 2017.

In FY 2016, the NanoCore co-organized the sixth "Nanotechnology for Healthcare Conference" with the University of AR for Medical Sciences, University of AR at Fayetteville, University of AR at Little Rock, and the Winthrop Rockefeller Institute. The Conference brought together international researchers and experts focused on human disease diagnostics, therapeutics, and prevention using nanotechnology. The Conference also covered approaches to develop international standards and methods for measuring nanomaterials and their impact. The keynote address was delivered by the 1996 Nobel Laureate in Chemistry, Sir Harold Kroto.

The 2016 Global Summit on Regulatory Science with the theme of "Nanotechnology Standards and Applications" was hosted by FDA, the Global Coalition, and the AR Research Alliance at the NIH campus. Panel discussions and speaker presentations, including former FDA Commissioner Dr. Robert M. Califf, explored the most immediate research needs in nanotechnology science, measurement methods, and standards relevant to regulatory applications.

Cancer Research Collaborations

Through the same MOU between the State of Arkansas and FDA, a consortium of five Arkansas research universities with significant expertise and investment in bioinformatics, computational science, DNA research, animal research, and clinical research work closely with researchers at NCTR to improve liquid biopsies. Researchers are using DNA found in cell-free components of blood ─ such as plasma ─ to develop precision medicine treatments for lung cancer, and eventually lung-cancer screening to supplement conventional imaging.

This project will use data from the treatment of genetic mouse models of lung cancer along with clinical samples and data from lung-cancer patients to refine the liquid biopsy approach. This approach has lower risks to patients than standard cancer-based biopsies and is more rapid and convenient.

FUNDING HISTORY

Fiscal Year	Program Level	Budget Authority	User Fees
FY 2014 Actual	$62,488,000	$62,488,000	$0
FY 2015 Actual	$63,312,000	$63,312,000	$0
FY 2016 Actuals	$63,329,000	$63,329,000	$0
FY 2017 Annualized CR	$63,211,000	$63,211,000	$0
FY 2018 President's Budget	$60,211,000	$60,211,000	$0

BUDGET REQUEST

The FY 2018 Budget Request is $60,211,000 and is all budget authority. Budget authority decreases by $3,000,000 compared to the FY 2017 Annualized CR level. This reduction in budget authority will delay the progress or start of critical research projects on food safety issues such as food contamination, dietary supplements, and antimicrobial resistance – delaying advances in regulatory science.

However, the FY 2018 budget request allows NCTR to conduct ground-breaking research to support the FDA Strategic Goals to Enhance Oversight and Improve and Safeguard Access. These areas of research include emerging technologies and toxicology assessments required by FDA. 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, human microbiome, 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

Center: -$3.120 million (Food Safety)
As part of the FY 2018 Budget, NCTR will reduce FTE through attrition and will scale back investments in IT and other administrative savings and lower priority research. NCTR will also

prioritize to minimize impact on the most urgent applied research projects. It is the goal of FDA to minimize the impact of these reductions on FDA's core mission activities.

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 2017 Target	FY 2018 Target
263103: Conduct translational and regulatory research to advance the safety of products that FDA regulates *(Output)*	FY 2016: Developed a new *in vitro* FluoroJade-C cellular toxicity assay that is simple, fast, and appears to be applicable to different types of cells from a variety species. Validation of this approach is ongoing and a manuscript is under revision *(Target Met)*	1) Initiate super-high field 23Na-MRI feasibility experiments – establish novel neurotoxicity biomarker proof of concept 2) Report preliminary findings on the neurological effects of commonly used chemotherapy drugs doxorubicin and cyclophosphamide	Report initial findings concerning opioid exposure during prenatal development on neural precursor cells
263201: Develop science base for supporting FDA regulatory review of new and emerging technologies *(Output)*	FY 2016: Published data indicating the potentially harmful neurological effects of sevoflurane and identified neuroprotective effects of Acetyl-L-carnitine using minimally invasive imaging approaches *(Target Met)*	1) Provide data on the toxicity of graphene nanomaterials leading to guidance for FDA-regulation of nanomaterials 2) Identify and validate predictive biomarkers for nanomaterial-associated immunotoxicity	Conduct analysis and risk assessment of drug-nanocrystals on the human gastrointestinal tract
262401: Develop biomarkers to assist in characterizing an individual's genetic profile in order to minimize adverse events and maximize therapeutic care *(Output)*	FY 2016: Completed a study regarding the understanding and prediction of rare and unpredictable side effects. Four publications resulted from the study *(Target Met)*	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	Complete a study that will promote women's health by facilitating the development of personalized approaches to treat breast cancer

Measure	Most Recent Result / Target for Recent Result	FY 2017 Target	FY 2018 Target
264101: Develop risk assessment methods and build biological dose-response models in support of food protection *(Output)*	FY 2016: Completed research concerning the molecular interactions that occur during simultaneous infection of *Salmonella* and norovirus. The research findings could constitute a mechanism to explain why some individuals would sustain norovirus infection for months versus the 2-3 days normally observed *(Target Met)*	Develop bioinformatics methods in support of microbial pathogen characterization and food protection	Provide data on how exposure of the human gastrointestinal tract to low concentrations of antimicrobial veterinary drug residues in food will affect intestinal bacteria and intestinal permeability of the consumer
263104: Use new omics technologies to develop approaches that assess risk and assure the safety of products that FDA regulates *(Output)*	FY 2016: Developed a method to detect biomarkers, in this case extracellular vesicles (EVs), in easily obtainable body fluids such as blood and urine. EVs are small membrane-bound bodies that are highly involved in cellular communication. The results of this study were published in *Biomarkers of Liver Disease (Target Met)*	Finalize research to identify translational biomarkers to aid in prevention and/or early detection of Drug Induced Liver Injury induced by FDA-regulated products	Using a multi-omics approach, identify an antimicrobial resistance marker of *Staphylococcus aureus* associated with antimicrobial-coated medical devices commonly used in a hospital setting
263102: Develop computer-based models and infrastructure to predict the health risk of biologically active products *(Output)*	FY 2016: A data mining approach was developed that clusters patients into biomarker subgroups. Each subgroup corresponds to an optimal liver cancer treatment regimen *(Target Met)*	Develop and refine FDA Label with new functionality based on feedback from FDA reviewers and scientists	Develop a novel data mining and data visualization method for safety surveillance of the FDA Adverse Event Reporting Systems (FAERS). FAERS contains adverse drug reaction reports submitted mandatorily and voluntarily by patients, health care professionals, and manufacturers to support post-market drug safety surveillance

PROGRAM ACTIVITY DATA TABLE

Program Workload and Outputs	FY 2016 Actual	FY 2017 Annualized CR	FY 2018 President's Budget
Research Outputs			
Research Publications	160	155	170
Research Presentations	148	148	135
Patents (Industry)	5	5	5
Leveraged Research			
Federal Agencies (Interagency Agreements)	3	3	3
Nongovernmental Organizations	19	19	19
Active Research Projects	165	160	154

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