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 has an outstanding scientific reputation worldwide. NCTR supports FDA’s strategic priorities to:

- Advance regulatory science to promote product safety, efficacy, quality, and innovation
- Enhance medical product safety, efficacy, quality, and innovation
- Enhance food safety.

NCTR enhances FDA’s basis for sound, science-based regulatory decisions and strengthens public-health assurance by:

- Accelerating FDA’s capability to manage, analyze, and interpret research data generated from new technologies using bioinformatics
- Understanding the risks and benefits to the American public of nanoscale materials being used in FDA-regulated products
- Expanding imaging capabilities to reduce the need for costly and dangerous surgical procedures and to prevent recurring illness
- Providing improved understanding of a contaminant’s toxicity so FDA can issue improved safety guidelines
- Identifying adverse effects earlier in product development
- Identifying individualized therapies using biomarkers – to lower costs for industry and consumers
- Developing new methods for rapid-detection of contaminants in FDA-regulated compounds
- Providing strategies to reduce pathogens and identify contamination sources in the food supply in support of the Food Safety Modernization Act (FSMA)
- Imparting research knowledge, technical advice, and research training through global collaborations like the Global Summits on Regulatory Science.

NCTR’s top three accomplishments support Advancing Regulatory Science (ARS) accomplishments, including two that support the ARS Strategic Plan goal to Improve Product Development and Patient Outcomes. The third accomplishment supports the ARS goal to Promote Global Interactions.

The following, selected accomplishments demonstrate NCTR’s delivery of its regulatory and public...
health responsibilities within the context of current ARS Strategic Plan priorities.\textsuperscript{31}

**Improve Product Development and Patient Outcomes**

Bioinformatics is an interdisciplinary field that uses software tools to develop and improve methods for storing, retrieving, organizing, and analyzing large quantities of biological data. FDA uses bioinformatics to increase understanding of biological processes by extracting results from large amounts of raw data. FDA can then use this data to improve product development and patient outcomes.

NCTR develops, provides training for, and makes available new bioinformatics tools to FDA and the international 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 for safety assessments and risk analysis. Some examples of NCTR’s uses of bioinformatics follow.

**ArrayTrack™ – FDA’s Bioinformatics Infrastructure**

The foundation of NCTR’s bioinformatics infrastructure is ArrayTrack™, an NCTR-developed database and data-analysis tool. ArrayTrack™ includes tools openly available to scientists, such as:

- SNPTTrack – measures the impact of genetic variation on drug treatment and personalized medicine
- Endocrine Disruptor Knowledge Base (EDKB) – a database of roughly 8,000 chemicals with endocrine disruptor activity data
- Estrogenic Activity Database (EADB) – assembles data from a variety of data sources and contains 18,114 estrogenic-activity data points collected for 8,212 chemicals tested in 11 different species.

**FDALabel Database – Analyzing Drug Labels**

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 drug-label information. Using the set of approximately 50,000 FDA-approved drug labels, FDALabel enhances drug-safety assessments for demographic subgroups. These subgroups allow for personalization of treatment in the clinical setting.

Approximately 400-500 new or updated drug-labels with information about product indications, target populations, and adverse drug reactions are added weekly to an FDA product-labeling database. This rapid growth poses a challenge for FDA staff members who routinely review labeling for safety and effectiveness data by demographic subgroups. FDALabel addresses this challenge. In fact, user statistics show that the number of active users for FDALabel has tripled in the last two years.

In 2013, NCTR scientists refined FDALabel by collaborating with CDER and CBER to integrate FDALabel with the Medical Dictionary for Regulatory Activities (MedDRA). Additionally, NCTR compared the results of manually extracted MedDRA terms with those that were extracted using computer programs. The results validated the performance of the automated MedDRA-term extraction feature. This integration allows rich resources of adverse drug-reaction information in FDALabel to be accessed and used in drug reviews and research.

**Drugs and Adverse Events**

\textsuperscript{31} Please visit [FDA.gov](https://www.fda.gov) for additional program information and detailed news items.
Also in support of FDASIA, NCTR scientists and CDER have developed an algorithm to identify the similarities and differences among drugs and adverse events in the FDA Adverse Events Reporting System database. The algorithm identifies associations between subsets of drugs and adverse events which analysts can then investigate to identify unrecognized adverse-event associations. In FY 2013, the analysis results of a sample dataset consisting of 193 cardiovascular drugs with 8,543 adverse events were published in the Journal of Biopharmaceutical Statistics (2013, 23:146-160) as an illustration.

NCTR and scientists from Germany’s Hannover Medical School used the algorithm to analyze 164 FDA-approved oral medications and showed an association of high daily doses with significant risk for drug-induced liver injury (DILI), known as a “rule of two.” This “rule of two” can be used to estimate risk for DILI better than by dose alone.

NCTR is developing other mathematical models to predict how effective a regulated drug will be or if serious adverse drug reactions can be anticipated based on a patient’s genetic make-up. These models can be implemented in an online knowledge base to alert reviewers, physicians, and patients of the potential for a drug to cause a serious adverse drug reaction in individuals with particular genetics before the drug is prescribed to the patient. With this information, FDA can offer patients and their health providers valuable information as to whether to use a particular drug.

Also, instead of withdrawing a drug that may have adverse reactions in certain patients, FDA can require the manufacturer to include appropriate warnings and to specify patient-marker criteria for prescribing it.

**Identifying and Developing Biomarkers**

Another tool for predicting FDA-regulated product toxicity is biomarker development. A biomarker indicates a biological state or condition that is measurable in human tissues, cells, or fluids. Biomarkers can be an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. NCTR scientists continue research to identify new biomarkers to identify toxicity of FDA-regulated products sooner and to provide personalized medicine solutions.

NCTR is conducting research to identify more sensitive and specific biomarkers of chemical-driven liver damage. This research identifies compounds not typically identified as being toxic to the liver. A finding from this work is that urinary microRNA, found in all cells, may be useful to health providers as a biomarker of overall liver injury and by FDA for the classification of specific toxicants. In fact, the NCTR publication titled “Identification of Urinary microRNA Profiles in Rats That May Diagnose Hepatotoxicity” (Toxicological Sciences, 2012, 125: 335-344) received Honorable Mention for the 2013 Best Paper Award by the Society of Toxicology (SOT) Board of Publications. The article reported the identification of a number of microRNAs (miRNAs) with elevated levels in the urine in the liver of animals treated with liver-toxic compounds.

NCTR scientists have also demonstrated that exposure to chemical carcinogens results in altered gene expression which may be used as a biomarker for cancer-risk assessment, and that treatment of a lung epithelial-cell line with cigarette smoke condensates resulted in changes in a number of critical genes shown to be involved in lung-cancer development. These results suggest that gene changes could serve as early biomarkers of harm due to cigarette smoke exposure.

Molecular biomarkers are being developed to identify drug-induced heart damage. These molecular biomarkers can be used to predict harmful effects of drugs during safety evaluations, to reduce or reverse cardiac injury, and to improve therapeutic patient treatment. Additionally, NCTR has been running parallel studies in zebrafish and nonhuman primates to identify critical biomarkers for studying pediatric products. While conducting a zebrafish study, NCTR scientists found that some compounds with little inherent toxicity, like L-carnitine, can have remarkable protective effects against the toxicities induced by general-anesthetic agents.

**Enhance Product Safety**
Using scientific tools like mathematical models and bio-imaging, NCTR provides FDA with data to enhance the safety of its regulated products. Both tools are noninvasive. Bio-imaging, for example, is a noninvasive technique, where you can visualize biological processes in “real time” with as little interference as possible with life processes.

**Bisphenol A (BPA)**

Several published studies have raised concern about the potential toxicity of certain substances at sensitive developmental stages in humans. BPA is an example of a substance that has aroused concerns recently. To provide FDA unbiased information, NCTR scientists developed a mathematical model in FY 2013 to predict BPA’s age-dependent effects and has shown that BPA exposures in very young rats over-predicts the effect on human infants. Results of this study were published in July 2013, in *Toxicology and Applied Pharmacology* (Vol. 270–1, July 2013, 45-59).

NCTR scientists will continue to develop data on BPA in fetal, neonatal, and adult rodent and nonhuman primate models. They will then combine data from these animal models with human data for predictive modeling of tissue exposures to BPA from food-contact materials, medical devices, and other sources.

**Pediatric Anesthetics**

The effect of pediatric anesthetics on children is an important area of research at NCTR. Advancements at NCTR’s bio-imaging facility using NCTR-developed bio-imaging tools allows FDA to gather information not previously obtainable to help the medical community understand the relationship between the amount, type, duration, and frequency of pediatric-anesthetic use and its adverse effects on children. NCTR scientists have extended their original findings with pediatric anesthetics ketamine, isoflurane, and nitrous oxide to include propofol and sevoflurane. During the studies, scientists repeatedly find that acetyl-L-carnitine provides neuroprotective properties when given prior to and during pediatric anesthesia. This protective effect occurs in a variety of species. FDA will use this data to establish guidelines to reduce anesthetic-induced neurological toxicity.

**Magnetic Resonance Imaging (MRI)**

Additionally, NCTR is developing methods to validate MRI scans. These methods may help distinguish between an adverse event, such as a tumor, and a normal event, such as scar tissue, without invasive surgery and may lead to the development of new noninvasive biomarkers that offer the possibility of better diagnosis with less risk and cost to the patient.

**Protect the Food Supply**

Patient cost for treatment of foodborne illnesses is a heavy burden on the U.S. economy. NCTR supports FSMA by identifying food-related health hazards and defending the food system, thus decreasing the frequency and severity of food- and feed-borne illness outbreaks and diminishing the negative economic effect.

**Antimicrobial Resistance**

Supporting FSMA, NCTR – in collaboration with the Marshfield Clinic Research Foundation and China Agricultural University – characterized antimicrobial genes from *Salmonella enterica*, a foodborne pathogen. Researchers found that multiple genes were resistant to the same antimicrobial and that a high number of genes were able to transfer resistance to other genes for at least six antimicrobials. This finding shows that antimicrobial resistance can be transferred from resistant organisms to those that were not previously resistant, leading to an increased public-health concern. The results of these studies were published in *PLoS One* (7(12): e51160, doi:10.137/journal.pone.0051160) and *Foodborne Pathogens and Diseases* (doi: 10.1089/pd.2012.1455). Additionally, DNA sequences from these studies were deposited in the GenBank database as a resource for other researchers.

**Bioterrorism**
NCTR and the Illinois Institute of Technology, have shown that the thermal stability of ricin – a lethal protein toxin and potential bioterror agent – was greater in yogurt and yogurt-containing fruit drinks compared to other foods tested, such as milk, infant formulas, and fruit juices. Although the toxins in ricin may be inactivated using heat, these research results show that the pH level of the ricin-containing product influences the effectiveness of the heating process to detoxify the ricin. The results of this study were published in August 2013, in *Food and Chemical Toxicology* (Vol. 58, Aug 2013, 116-123).

**Evaluate Innovative Emerging Technologies**

Nanotechnology is science, engineering, and technology conducted at the nano scale. This emerging trend of using extremely small materials has the potential to be used in a broad array of FDA-regulated products.

New nanotechnology information becomes available every day and must be proactively assessed to protect the American public. Right now NCTR is conducting nanotechnology research. The NCTR-ORA Nanotechnology Core Facility generates data used by FDA reviewers to assess the safety and responsible development of products using nanomaterials and aids the development of guidelines for the safe and effective use of these materials in drug products, devices, foods, cosmetics, and dietary components.

**Nanosilver**

NCTR scientists are studying various routes of exposure to nanomaterials and the effects on the body. This information provides a better understanding of nanomaterials, which can then be used to inform regulatory decisions.

Exposure to nanoparticles – nanosilver especially, because of its antimicrobial use – from food or food packaging is the greatest nano-related risk to consumers. Scientists are studying nanosilver ingested by rodents for hazard identification and developing methods to measure nanosilver migration, providing data for regulatory decisions. In FY 2013, NCTR scientists found that some nanomaterials such as nanosilver interact with blood-brain-barrier cells and generate an adverse reaction.

**Promote Global Interactions**

**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, now in its third year. NCTR hosted the two day third annual Global Summit in September, 2013 with international participants with a focus on nanotechnology, providing an opportunity for government, industry, and academic-research scientists to objectively assess the utility of emerging technologies, such as nanotechnology, imaging, and omics for translational science and personalized medicine, and how to translate these technologies into real-world applications.

To engage the global community and harmonize strategy via global collaboration, the Summit is held in a different location each year. The Summit prompted the development of a Global Coalition for Regulatory Science Research with scientific experts and Federal executives from around the world who collaborate to build knowledge of and promote regulatory science, define research needs, and strengthen product safety worldwide.

**Bioinformatics Collaborations**

NCTR and the Arkansas State University system are working together to establish a virtual Arkansas Bioinformatics Center to build bioinformatics capabilities. In FY 2013, there have been three planning meetings between NCTR, representatives from Arkansas colleges, and the Arkansas Research Alliance.
Nanotechnology Collaborations

Supported by a Memorandum of Understanding with FDA and the State of Arkansas, NCTR is collaborating with five Arkansas research universities on a virtual center for nanotechnology and nanotoxicology. In FY 2013, these partners held a consortium to discuss studies to synthesize the carbon-based nanomaterial, graphene, similar to the compound anticipated to be found in FDA-regulated products.
FUNDING HISTORY

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Program Level</th>
<th>Budget Authority</th>
<th>User Fees</th>
</tr>
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<tbody>
<tr>
<td>FY 2011 Actual</td>
<td>$60,563,000</td>
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<td>FY 2012 Actual</td>
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<td>FY 2014 Enacted</td>
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<tr>
<td>FY 2015 Budget Request</td>
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</table>

BUDGET REQUEST

The FY 2015 Budget is $58,998,000, which is all budget authority. This amount is $3,496,000 less than the FY 2014 Enacted level. This reduction in budget authority will delay the progress or start of critical research projects, delaying advances in science.

With this budget request NCTR will:

- conduct innovative research
- develop new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of regulated products
- integrate comprehensive toxicology safety assessments maximizing existing and emerging technologies
- keep pace with the changing landscape of regulatory science
- provide valuable research data on products using new technologies
- conduct studies and create tools to help FDA better understand data submissions by product sponsors that are generated using new technologies.

The FY 2015 Budget allows NCTR to continue its ground-breaking research to support the ARS priorities of Evaluating Emerging Technologies, such as nanotechnology, bio-imaging, bioinformatics, and biostatistics. In each of these areas, investments have been made in recent years to build the capabilities and expertise for the benefit of FDA and ultimately, the American public. These funds will allow such efforts to continue and will give the programs and associated projects the opportunity to mature. Additionally, the advances made by NCTR in the area of biomarker identification can continue in support of the ARS Priority to Improve Product Development and Patient Outcomes by tailoring medical products to provide more personalized medicine.

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.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Most Recent Result / Target for Recent Result</th>
<th>FY 2014 Target</th>
<th>FY 2015 Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>263103: Conduct translational and regulatory research to advance the</td>
<td>FY2013: 1) Findings on prolonged exposure</td>
<td>1) Complete a simulation protocol to help reduce the uncertainty in the risk-</td>
<td>1) Complete research that will provide information on toxicity of nanoscale</td>
</tr>
<tr>
<td>safety of products that FDA regulates (Output)</td>
<td>to certain anesthetic agents have been</td>
<td>assessment of BPA</td>
<td>silver</td>
</tr>
<tr>
<td></td>
<td>published and presented at several</td>
<td>2) Evaluate the effects of methylphenidate, a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>scientific conferences</td>
<td></td>
<td>2) Present findings on</td>
</tr>
<tr>
<td>Measure</td>
<td>Most Recent Result / Target for Recent Result</td>
<td>FY 2014 Target</td>
<td>FY 2015 Target</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------------------------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>263201: Develop science base for supporting FDA regulatory review of new and emerging technologies <em>(Output)</em></td>
<td>(Target Met)  2) Identified specific genetic factors that may lead to varying vulnerability seen with a progressive form of liver disease <em>(Target Met)</em>  3) Characterized the virulence and antimicrobial resistance of <em>Salmonella Enteritidis</em> and Heidelberg isolates <em>(Target Met)</em></td>
<td>drug for the treatment of Attention-Deficit Hyperactivity Disorder, using bioimaging techniques</td>
<td>research aimed at identifying biomarkers(biological indicators) to predict the effects of cancer drugs on the heart</td>
</tr>
<tr>
<td>264101: Develop risk assessment methods and build biological dose-response models in support of food protection <em>(Output)</em></td>
<td>FY2013:  1)14 novel biomarkers were identified when using a combination of next generation sequencing, microarray, and bioinformatics <em>(Target Met)</em>  2) Showed that divergent strains of coronavirus circulate in regions of Arkansas <em>(Target Met)</em>  3) Developed an FDA-related nanoparticle for study <em>(Target Met)</em></td>
<td>Identify an assay to detect infectious norovirus in contaminated foods</td>
<td>Initial results issued on research to find a robust and convenient method to verify the potency of potential bioterrorism agents in food supply</td>
</tr>
<tr>
<td>262401: Develop biomarkers to assist in characterizing an individual’s genetic profile in order to minimize adverse events and maximize therapeutic care <em>(Output)</em></td>
<td>FY2013: Published results that found potential for new breast cancer therapy using epigenetic approach <em>(Target Met)</em></td>
<td>Determine if some drugs cause a higher incidence of liver toxicity in women than men</td>
<td>1) Complete pilot project that will promote women’s health by facilitating the development of personalized approaches to treat breast cancer  2) Evaluate serum metabolic biomarkers to determine whether they are correlated to acute kidney illness diagnosis and prognosis</td>
</tr>
</tbody>
</table>
Measure | Most Recent Result / Target for Recent Result | FY 2014 Target | FY 2015 Target
--- | --- | --- | ---
263104: Use new omics technologies to develop approaches that assess risk and assure the safety of products that FDA regulates \((Output)\) | FY2013: 1) Developed a centralized system of both data and predictive models useful for research and regulation concerning drug-induced liver injury (Target Met) 2) Algorithm developed that characterizes similarities and differences among drugs in an FDA adverse event database (Target Met) | Determine if miRNA(found in easily-obtained body fluids) exhibit superior biomarker properties that can be used for indicating drug induced liver injury | Use a new approach—antibody microarray analysis—to identify proteomic changes that may precede neurotoxicity
263102: Develop computer-based models and infrastructure to predict the health risk of biologically active products \((Output)\) | FY2013: 1) Published review on performance of major next generation sequencing systems and analyses related to cancer 2) Developed suite of pharmacogenetic software tools | Find new uses for existing and abandoned drugs | Establish a modeling tool that can be used to predict drug-repurposing opportunities

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

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

Findings on prolonged exposure to certain anesthetic agents have been published and presented at several national and international scientific conferences including two FDA advisory panel meetings and are enabling clinical studies by supplying exposure, endpoint, and prevention approaches to improve the safe use of anesthetics in children. Research in the field of children’s anesthetics is ongoing at NCTR and continued evaluation of the neurotoxicity of sevoflurane and propofol is a goal for 2014.

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

A combination of next-generation sequencing, microarray, and bioinformatics techniques was used to identify 14 novel biomarkers in an animal model. The research adds to the growing knowledge of using miRNA - found in easily-obtained body fluids - as biomarkers for the early detection of diseases and adverse drug events. In 2014, NCTR will conduct research to define the miRNA biomarker genes that are associated with carcinogen exposure.

**Personalized Medicine**

Investigators at NCTR conducted experiments that highlighted the potential for a new epigenetic approach in improving breast-cancer therapy by targeting cancer genes using miRNA. The method shows promise as a noninvasive breast cancer therapy. These findings were published in the Journal of Carcinogenesis in July 2013. Future plans for research in the area of personalized medicine include determining whether some drugs cause a higher incidence of liver toxicity in women than men and completing research that promotes women’s health with personalized approaches to breast cancer.
**PROGRAM ACTIVITY DATA**

National Center for Toxicological Research Program Activity Data (PAD)

<table>
<thead>
<tr>
<th>Workload and Outputs</th>
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<th>FY 2014 Estimate</th>
<th>FY 2015 Estimate</th>
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<tr>
<td><strong>Active Research Projects</strong></td>
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