U.S. Food & Drug Administration

National Center for Toxicological Research Annual Report 2019

2019 Annual Report for FDA/NCTR

Vision, Mission, and Goals

Vision

The U.S. Food and Drug Administration's National Center for Toxicological Research is a global resource for collaboration—providing consultation, training, and innovative scientific solutions in support of FDA's mission to improve public health.

Mission

NCTR conducts scientific research to generate data for FDA decision making and develops and supports innovative tools and approaches that FDA uses to protect and promote individual and public health.

NCTR Research Goals

- Advance scientific knowledge and tools required to support personal, animal, and public health
- Enhance collaborations with other FDA centers
- Promote global interactions in regulatory science

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PREFACE

Message from the Director

The National Center for Toxicological Research (NCTR) is the U.S. Food and Drug Administration's (FDA) premier laboratory research center focused on all FDA-regulated products. NCTR's primary goal is to support FDA, a critical component of the Department of Health and Human Services (HHS), in its efforts to promote and protect the health of the American public.

NCTR holds a unique and foundational position at FDA because it is the only center that supports all FDA offices and product centers with the essential toxicological research they need to conduct their scientific activities. NCTR's work has been critical to the development and evaluation of emerging toxicological methods and other new technologies that play such a large role in FDA's regulatory decision-making.

We invite you to learn how NCTR scientists are supporting the agency in advancing the innovative tools and approaches that are vital to FDA's predictive capability and our ability to predict risk and efficacy.

/s/

William Slikker, Jr., Ph.D., Director, NCTR

About the Annual Report

Thank you for your interest in NCTR! The 2019 annual report highlights NCTR's accomplishments for the 2019 calendar year. Included are links to the NCTR pages on FDA.gov and various scientific publications are referenced.

Note: This document is the text-only version to meet 508-compliance; if you would like to view the visually interactive report, please visit *https://www.fda.gov/about-fda/national-center-toxicological-research/nctr-annual-reports.*

NCTR Organization Structure

NCTR Leadership

Center Director, FDA/NCTR: *William Slikker, Jr., Ph.D.*

Associate Director, Science and Policy, Office of Research: *Tucker Patterson, Ph.D.*

Associate Director Office of Scientific Coordination: *Bradley Schnackenberg, Ph.D.*

Executive Officer Office of Management: *Winona Cason*

Associate Director Office of Regulatory Compliance & Risk Management: *Rajesh Nayak, Ph.D.*

Associate Director Regulatory Activities: *Donna Mendrick, Ph.D.*

NCTR Research Division Directors

Biochemical Toxicology: *Frederick Beland, Ph.D.*

Bioinformatics and Biostatistics: *Weida Tong, Ph.D.*

Genetic and Molecular Toxicology: *Robert Heflich, Ph.D.*

Microbiology: *Carl Cerniglia, Ph.D.*

Neurotoxicology: *Sherry Ferguson, Ph.D.*

Systems Biology: *William Mattes, Ph.D., DABT*

Click here for more information about NCTR Research Divisions

NCTR at a Glance

Evolving Scientific Areas

- Microphysiological systems, organotypic models, and stem cells
- Microorganism detection in food, tobacco, and biological products
- Omics (genomics, metabolomics, proteomics, epigenetics)
- Translational and precision medicine
- Nanotoxicology
- Artificial intelligence (e.g., machine learning, text mining, in silico modeling)
- Microbiome and host interactions
- Perinatal and maternal health

NCTR Expertise

- Analytical chemistry
- Antimicrobial resistance and pathogenicity
- Reproductive and developmental toxicology
- Genetic toxicology assay development
- Neurochemistry
- Neuropathology
- Bio-imaging (MALDI, MicroPET, MRI, MRS, CT)
- Biomarker development
- Behavioral assessments
- Phototoxicology
- Bioinformatics and biostatistics (data mining)
- PBPK modeling

NCTR identifies new biomarkers of toxicity using traditional and innovative genomics, metabolomics, proteomics, epigenetics, and imaging technologies and approaches.

Facilities

***>1 million** square feet across 30 buildings*

- Nanotechnology Core Facility
- Inhalation Core Facility
- Phototoxicology Laboratories
- Bio-imaging Facility
- Animal Facilities

***>100** experimental laboratories operate on NCTR's research campus*

***>75** AALAC animal laboratories*

NCTR at a Glance

Numbers for 2019

Manuscript Submissions & Newsletter Subscriptions

Research performance is typically difficult to measure and quantify. One way NCTR measures research performance is by tracking how much NCTR research is being published in reputable scientific journals. Below are the publication numbers for 2019.

Number of NCTR Publications (2017-2019)

2019 – 134
2018 – 170
2017 – 155

NCTR also measures its research performance by tracking the number of visitors who subscribe to:

- **NCTR Research Highlights** – brief summaries of NCTR research accomplishments and activities, research publications, and special events.
- **NCTR Science Insights** – a newsletter sent periodically with a more comprehensive summary of NCTR research activities, accomplishments, collaborations, and special events.

If you are interested in subscribing to NCTR Research Highlights and/or Science Insights, please visit our website and subscribe with your email address.

NCTR Research Highlights & Science Insights Subscriptions

2019

- Total Subscriptions (Research Highlights and Science Insights) – 91,918
- Research Highlights Subscriptions – 48,807
- Science Insights Subscriptions – 43,111

2018

- Total Subscriptions (Research Highlights and Science Insights) – 86,311
- Research Highlights Subscriptions – 46,210
- Science Insights Subscriptions – 40,101

NCTR at a Glance (continued)

Numbers for 2019

NCTR Office of Management – Human Capital

NCTR's mission to support FDA has been challenging in recent years due to increased security requirements for non-U.S. citizens. This makes it difficult to recruit and retain a highly-trained and skilled workforce.

To help meet this challenge, NCTR leveraged Direct Hire Authority for several STEM occupations. A DHA is an appointing (hiring) authority that Office of Personnel Management (OPM) can give to FDA to fill vacancies when there is a critical hiring need or severe shortage of candidates. Through the use of DHAs and other recruitment flexibilities, hiring over the past couple of years has continued to remain steady. In 2019, NCTR filled 34 positions, including external hires, conversions from staff fellow to GS positions, backfills, and internal promotion opportunities for existing staff.

As a result of these efforts, NCTR has enhanced and expanded its scientific capacity and scientific expertise, while existing staff have been able to advance and serve in positions of increased scope and responsibility. This would not have been possible without the hard work and dedication of NCTR's Office of Management's Human Capital team in close partnership with FDA's Office of Talent Solutions.

Total Number of Government Positions Filled (2017-2019)

2019 – 34

2018 – 32

2017 – 35

Federal Employee Viewpoint Survey (FEVS)

The annual FEVS is administered each year by the Office of Personnel Management (OPM). The EVS is designed to provide valuable information on employee satisfaction, commitment, and engagement. The EVS workgroup has made significant strides in recent years to increase NCTR's participation rate, address issues that impact the workplace climate for NCTR employees, and lead morale-boosting events.

NCTR's EVS workgroup developed and implemented several center- wide strategies to increase survey participation, which resulted in an 80.5% participation rate—**2nd highest in FDA and 16% higher than 2018!**

NCTR at a Glance (continued)

Numbers for 2019

FDA-TRACK NCTR

FDA-TRACK is FDA's agency-wide performance management system that monitors FDA centers and offices through key performance measures and projects. NCTR has several key research projects and other related metrics that are tracked and published on the public-facing FDA.gov site.

Explore the progress NCTR is making towards its strategic priorities.

2019 Research Collaborations

A critical component of NCTR's science portfolio is collaborations with other FDA centers to leverage knowledge and to establish partnerships. Expertise from each center has contributed to the development of critical scientific projects that have focused on the regulatory needs of the agency. 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.

167 of 229 (72%) of NCTR ongoing projects are collaborative with another organization.

133 of 229 (58%) are collaborative with other FDA Centers/Offices.

34 of 229 (15%) are collaborative with organizations outside of FDA including, but not limited to:

- *National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/ NTP)*
- *National Institutes of Health (NIH)*
- *United States Department of Agriculture (USDA)*
- *University of Arkansas for Medical Sciences (UAMS)*
- *University of Arkansas at Little Rock (UALR)*

NCTR Ongoing Projects – Collaborations

CBER – 6%

CDER – 39%

CDRH – 10%

CFSAN – 7%

CTP – 4%

CVM – 5%

ORA – 4%

NTP-IAA – 7%

All Other – BAA/Tech Transfer – 10%

University/Academia – 8%

Collaborations

Center for Drug Evaluation and Research (CDER)

In 2019, NCTR continued to strengthen its collaborations with the Center for Drug Evaluation and Research (CDER) to help address important and timely questions that influence decision making for FDA-regulated products. The NCTR-CDER partnership continues the synergy between the centers and the researchers furthering FDA's regulatory-science knowledge.

NCTR-CDER InterCenter Projects

As shown on the previous page, out of all NCTR collaborations with FDA centers, CDER makes up 52% of those projects. Each year, CDER also directly funds research to be conducted at NCTR. Rigorous review and ranking take place to ensure that any funded research strongly aligns with CDER research priorities. In 2019, a variety of research projects were funded through this mechanism. The projects covered topics in the follow sub-sections.

Opioids

NCTR, in collaboration with CDER, continues to generate data on exposure of brain cells to opioids during perinatal development. In 2019, hydrocodone, codeine, oxycodone, and hydromorphone were evaluated along with the positive control, valproic acid. Preliminary results suggest tested opioids have minimal effect on early stem- cell growth and development. Screening of additional opioids including morphine, methadone, buprenorphine, and fentanyl are planned for 2020.

Another opioid-related project in collaboration with CDER began in 2019 and uses computational models to assess opioid structure. This project should create a better understanding of the structural requirements associated with a strong addiction potential and would allow an accurate prediction of this potential for opioids and other structurally diverse chemicals. This technology could be used to prioritize the testing of chemicals with strong addiction potentials (such as novel compounds and synthetic opioids), thus shortening the FDA regulatory-review process. This project is expected to be finalized in 2021.

While it has been suggested that multiple neurotransmitters play a role in the abuse-related effects of opioids, a comprehensive analysis of these effects in response to opioids has yet to be established. It is hoped that imaging technologies may help delineate an opioid's mechanism of action. In late 2019, NCTR began a project that will attempt to use imaging technologies to reveal the abuse-related effects of opioids.

Compounding

A compounding-related research project at NCTR will develop and validate a novel mass-spectrometry approach for analyzing crude samples without purification. This project is in collaboration with CDER's Division of Pharmaceutical Analysis (DPA). DPA has shown

the possible utility of this analysis for examining components in creams, such as those developed in pharmaceutical compounding. Clearly a key element in the safety and efficacy of a

compounded product is quality; as noted on FDA's webpage, Compounding and the FDA: Questions and Answers, "poor compounding practices can result in serious drug quality problems, such as contamination or a drug that contains too much active ingredient." A rapid means for assessing the components and contaminants of a compounded product would provide a valuable tool for protecting public health. This re- search is expected to be completed in 2022.

Sunscreens

In 2019, NCTR continued a CDER-collaborative study entitled "An assessment of the interactions of nanoscale (TiO2 and ZnO) materials used in sunscreens on the skin microbiome." Approximately, 95 million U.S. women aged 18 and older have used cosmetics. Recently, via the Safe Cosmetics Act of 2010, Congress is targeting regulation on cosmetics. Nanomaterials are now used in many cosmetic products that are already on the market including lipsticks, anti-aging creams, sunscreen, eye shadow, moisturizer, and foundation, and the number of nanomaterial-containing products are increasing rapidly. There are potential risks for externally applied cosmetics and sunscreens containing nanoscale materials to impact the microbial ecology of the skin. The lack of knowledge about the effects of nanoscale materials on human-skin microbiota makes this a critical area of research. This study will enhance FDA's scientific understanding of the safety and toxicity of the nanomaterials in cosmetics and provide data to be taken into consideration for safety assessment.

Collaborative Support of the Sunscreen Innovation Act

NCTR management met September 2019 to finalize the CDER/NCTR Memorandum of Understanding (MOU) regarding over-the-counter drug review; the agreement was sent to CDER for signature. The MOU ensures that both CDER and NCTR continue their collaborative relationship in support of the Sunscreen Innovation Act.

Other Areas of Study

Other research studies include the following:

- Validating the rat Pig-a assay for regulatory use: Determining the molecular basis of mutants detected in the rat Pig-a gene mutation assay.
- Advance safety assessments of FDA-regulated products using high-throughput and high-content quantitative approaches in cultured human cells to evaluate genotoxicity.
- Comparative methods study for the detection of Burkholderia cepacia complex from non-sterile pharmaceutical products.
- Effects of the gaseous anesthetic, Desflurane, on the brain.

Collaborations

Center for Tobacco Products

The collaboration between Center for Tobacco Products (CTP) and NCTR provides the research data needed for FDA to support the regulatory authorities within the Family Smoking Prevention and Tobacco Control Act to protect public health. The tobacco regulatory science conducted at NCTR can be summarized in the following research areas.

Inhalation Toxicology

Inhalation toxicology studies are necessary to evaluate the dose-response toxicity of inhaled chemicals that are found in tobacco products or that form during the combustion process. The Center for Tobacco Products/NCTR Inhalation Toxicology Core Facility (InhaleCore) provides the technical expertise to conduct these inhalation studies in compliance with international test guidelines (e.g., Organization for Economic Co-operation and Development, OECD). In collaboration with CTP, the InhaleCore researchers study animal biological responses using various toxicological endpoints after they are exposed in a well-defined environment via nose-only inhalation. The research outcomes provide data to better understand and quantify the adverse health risks associated with humans using tobacco products, thereby supporting the FDA mission of regulating tobacco products.

Predictive Modeling

The collaboration between the NCTR and CTP modeling groups continued to develop a human physiologically-based pharmacokinetic (PBPK) model for nicotine. Using biomarker and dose-response data from existing studies and scientific literature, this model will describe the internal dose metrics of nicotine for multiple exposure pathways and assess the nicotine exposure-response relationship across different tobacco product types.

Collaborations

Center for Food Safety and Nutrition

Artificial Intelligence (AI)

In collaboration with the Center for Food Safety and Nutrition (CFSAN) and the Office of Regulatory Affairs (ORA), NCTR scientists continued to develop an intelligent system for species identification of food-contaminating beetles. Species identification is important to risk assessment for food filth inspection and analysis. Insects are often broken into small fragments during food processing and thus species identification by insect fragments is extremely difficult, even for food analysts with years of on-job experience. This lack of reliable and efficient methods becomes more difficult as vast amounts of processed food products are imported from places where the alternate preventive inspection of facilities is usually not conducted for a variety of reasons.

This project developed a cost-effective and intelligent system for the species identification of storage pests by examining the patterns retrieved from their hard wing fragments in FDA-regulated food products. The new system integrated the latest advancements in image analysis, artificial intelligence, and information technology. The system decreased the time and cost to identify storage pest-fragments that contaminate food products, thereby greatly increasing the number of food samples that FDA can examine for extraneous materials. A large set of high-quality images were collected and thus improved the overall accuracy of our deep learning model to over 90 percent. Together with a new and more flexible user interface, the updated model will be given to ORA food analysts for field testing by the end of FY 2020. Recent publications related to this project can be found in *Computers and Electronics in Agriculture* and *Scientific Reports*.

Tattoo Inks

While tattoos have become more mainstream, tattoo ink manufacturers do not uniformly declare the ingredients on labels or in material safety data sheets. Therefore, there is a need to assess the safety of tattoo inks regarding toxic and allergenic elements. To this end, NCTR and CFSAN collaborated on a project that determined the concentrations of nine elements in a set of approximately 90 tattoo inks of various colors. This project was concluded in 2019.

Microblading & Permanent Makeup Inks

NCTR and CFSAN researchers focused on a microbial survey of microblading and permanent makeup (PMU) inks. The aim of this study was to provide strong scientific data on the microbiological safety of these products and to develop policies underlying possible enforcement actions. The team surveyed 47 microblading and PMU inks that were purchased from nine manufacturers (including four foreign manufacturers). Overall, results showed that commercial microblading and PMU inks available in the United States are contaminated with microorganisms including possibly pathogenic bacteria. They are less contaminated than tattoo inks.

Collaborations

Center for Veterinary Medicine

Antimicrobial Resistance (AMR)

NCTR scientists have demonstrated that when certain *Salmonella* strains were exposed to different concentrations of specific antibiotics, there was an increase in the rate of resistance. In collaboration with FDA's Center for Veterinary Medicine (CVM), NCTR scientists used techniques to better understand the diversity of organisms. NCTR scientists also studied the presence of plasmids— independent DNA molecules commonly found in cells—that can contribute to AMR and enhanced disease-causing ability. NCTR and CVM continue their efforts in this vastly understudied research area and are developing a database and analysis tool to better understand and control *Salmonella enterica* in foods and feed. A publication describing NCTR's and CVM's research in this area can be found in the *International Journal of Food Microbiology*. A related publication entitled "Draft Genome Sequences of 27 *Salmonella enterica* Serovar Schwarzengrund Isolates from Clinical Sources" can be found in *Microbiology Resource Announcements*.

Drug Residues

The use of veterinary antimicrobials in food-producing animals may result in antimicrobial drug residues (ADR) in edible tissues and meat products from the treated animal. The effect of ADR in the food supply on public health, regarding their impact on the human intestinal microbiome and potential to select for antibiotic-resistant bacteria in the gastrointestinal tract, is unknown.

To provide guidance for the safety of veterinary ADR in the human food supply, NCTR and CVM began a collaborative project to elucidate these unknowns. In 2019, NCTR and CVM continued their collaboration and published an article related to ADR and the human intestinal microbiome permeability in *Microorganisms*.

Virulence Gene Database

NCTR developed a virulence gene database and related analyses that assist in predicting virulence genes present in sequencing data. Also, a modern user-friendly front-end website was developed which provides features to view and manage the data collected along with providing a platform for future tool development.

Collaborations

Office of Regulatory Affairs

Automated Laboratory Information System (ALIS)

In collaboration with the Office of Regulatory Affairs (ORA), NCTR developed an initial prototype laboratory information management system (LIMS) for use in ORA laboratories. The ORA conducts reviews of domestic and foreign goods in 13 laboratories across the United States, using a mix of paper-based and digital components. The goal of the new ALIS system is to use modern technologies to simplify and automate, where possible, the ORA-data collection processes that are used daily in the ORA laboratories. NCTR developers assisted in creating unified laboratory standards, created data models for the system, developed new user interfaces, and created code to synchronize the new system data with existing digital components. NCTR developers worked closely with ORA staff to develop screens and workflows for the new systems. In 2019, an initial prototype for microbiology lab data collection was delivered after working extensively with ORA staff at Arkansas Laboratory on user interface and workflow requirements. The prototype was highly successful and further development is planned. Near the end of 2019, work on pesticides was begun, with NCTR developers traveling to Northeast Food and Feed Laboratory (NFFL) to gather requirements for the new work.

Collaborations

NIEHS/National Toxicology Program (NTP)

The National Toxicology Program (NTP) was established in 1978 to coordinate toxicology research and testing across the Department of Health and Human Services. The program was created to provide information about potentially toxic chemicals to health regulatory and research agencies, strengthen the science base in toxicology, and develop and validate improved testing methods. NTP consists of three core agencies that provide support for NTP activities:

- National Institute of Environmental Health Sciences (NIEHS/NTP)
- U.S. Food and Drug Administration's National Center for Toxicological Research (FDA/NCTR)
- Centers for Disease Control and Prevention's National Institute for Occupational Safety and Health (CDC/NIOSH)

In support of the NTP mission, NIEHS/NTP and FDA/NCTR established an Interagency Agreement (IAA) in 1992, facilitating the conduct of toxicology studies on chemicals or substances nominated to NTP that may be under the regulatory purview of FDA, to be studied using the unique resources and facilities at NCTR.

NCTR/NTP Quick Facts

- In 2019 NIEHS/NTP and FDA/NCTR had **10 active collaborative projects** under their IAA.
- The success of this IAA has led to **over 25 years of collaborative toxicity testing** on compounds of interest to FDA and NTP.
- The IAA program has led to the toxicity assessment and mechanism-of-action studies of many classes of chemicals including: **food contaminants, cosmetics, endocrine-disruptor compounds, food cooking by-products, dietary supplements, drugs, and anesthetics.**
- Notable chemicals studied as a result of the NCTR/NTP collaborative agreement: **Bisphenol A (BPA), Arsenic, Triclosan, and Acrylamide.**
- The research program conducted under the IAA resulted in the publication of 18 NTP Technical and Research Reports and over 250 peer-reviewed manuscripts.

Science Advisory Board

National Center for Toxicological Research

Toxicological Research, Science Advisory Board to NCTR

NCTR—in partnership with researchers from FDA centers, other government agencies, academia, and industry—provides innovative technology, methods development, vital scientific training, and technical expertise. The unique scientific expertise of NCTR is critical in supporting FDA product centers and their regulatory roles.

Purpose

The Science Advisory Board (SAB) to NCTR advises the NCTR Director in establishing, implementing, and evaluating the research programs that assist the FDA Commissioner in fulfilling his or her regulatory responsibilities. The Board provides an extra-agency review in ensuring that the research programs at NCTR are scientifically sound and pertinent.

Board Membership

The Committee shall consist of a core of nine voting members including the Chair. Members and the Chair are selected by the Commissioner or designee from among authorities knowledgeable in the fields of toxicological research. Members will be invited to serve for overlapping terms of up to four years. Almost all non-Federal members of this committee serve as Special Government Employees. The core of voting members may include one technically qualified member, selected by the Commissioner or designee, who is identified with consumer interests and is recommended by either a consortium of consumer-oriented organizations or other interested persons.

The SAB to NCTR advises the Commissioner or designee in discharging responsibilities as they relate to helping to ensure safe and effective drugs for human use and, as required, any other product for which the FDA has regulatory responsibility.

2019 SAB Meeting

The 2019 meeting of the NCTR SAB took place in December 2019 in Little Rock, Arkansas. The meeting lasted two days and covered a variety of topics such as:

- Overview of NCTR
- Overview of NCTR Research Divisions
- Genetic and Molecular Toxicology Review
- NCTR Collaborations with FDA Centers

More information on the 2019 SAB meeting can be found on our website.

Perinatal Health Center of Excellence

2019 PHCE Highlights

- **Congressional funding** for the PHCE was provided in NCTR FY19 budget.
- **14 PHCE proposals** were selected to be funded in FY19 and FY20.
- **PHCE** Primary Investigators represent **CDER, CDRH, CBER, CFSAN, and NCTR**.
- In September 2019, NCTR held a **PHCE Research Day** at White Oak which included presentations for all 14 projects.

In FY 2019, with Congressional support, NCTR fully implemented the Virtual Center of Excellence for Perinatal and Maternal Pharmacology and Toxicology – also known as the FDA Perinatal Health Center of Excellence (PHCE). The perinatal period is the period-of-time including pregnancy, childbirth, and infant/child development. The PHCE was accepted by the FDA centers and ORA representatives with the goal to strengthen the scientific basis of decision making of FDA-regulated products used during pregnancy and in premature infants, newborns, and children.

Pregnant women and preterm and term offspring represent understudied populations; many FDA- regulated products provided to neonates and infants, or provided to or used by pregnant mothers, have not been studied extensively in these populations. The PHCE will work to fill knowledge gaps about safety, efficacy, or potential toxicity that currently exist.

In FY 2019, the PHCE leadership council, with representatives from all FDA centers and ORA, rigorously reviewed 22 submissions and selected 14 proposals to be funded for two years by investigators representing CBER, CDER, CDRH, CFSAN, NCTR, OC, and ORA —all with either internal or external collaborators have begun working on their funded PHCE studies and will continue into FY 2020. ***Additional information about the PHCE can be found on our website.***

Global Summit on Regulatory Science (GSRS)

The Global Summit on Regulatory Science (GSRS) is an international conference for discussion of innovative technologies and partnerships to enhance translation of basic science into regulatory applications within the global context. The conference provides an opportunity for scientists from government, industry, and academic-research communities to objectively assess the utility of emerging technologies (such as nanotechnology, imaging, omics for translational science, personalized medicine, medical product safety, and food safety) for addressing regulatory-research questions and to discuss the best way to translate these technologies into real-world applications. The conference provides a platform where regulators, policy makers, and bench scientists from various countries can exchange views on how to develop, apply, and implement innovative methodologies into regulatory assessments in their respective countries, as well as harmonizing strategy via global collaboration. To engage the global community to address regulatory-science research and training needs, GSRS will be held in different countries on an annual basis.

NCTR's Director serves as the co-chair of the Coalition's executive committee and works with the Coalition to promote global interaction. The Global Summit is led by the Global Coalition which is comprised of regulatory science leaders from around the world including Australia, Belgium, Brazil, Canada, China, Italy, Japan, Nigeria, Singapore, India, Korea, Thailand, and the U.S. The 10th Anniversary Global Summit will take place virtually in 2020. The meeting will focus on emerging technologies and their application to regulatory science.

Summary of GSRS19 – Lago Maggiore, Stresa, Italy

The 9th Global Summit for Regulatory Science (GSRS19) was held from September 24-26, 2019 in Italy at the JRC – European Commission. The meeting focused on on Nanotechnology and Nanoplastics and included over 200 scientists in attendance from 36 countries representing regulatory and research institutes along with academic and industry participants to present on the regulatory science perspective, current status, knowledge gaps and future outlook. The summit topics and sessions included plenary sessions on perspectives from regulatory agencies and others with parallel sessions on drugs, foods, devices, nanotoxicology, and standards.

The plenary session on nanoplastics brought together current state of the art in microplastics, the concerns, research efforts, potential health effects, emphasizing the lack of information and data on nanoplastics. There were pre- and post-meeting training sessions, lab tours of the Nanobiotechnology Center, and an American Society for Testing and Materials (ASTM) International E56 ASTM E56 meeting on nanotechnology standards.

For additional details, updates, abstract guidelines, agenda, and more visit [www.fda.gov/globalsummit.](www.fda.gov/globalsummit)

2019 NCTR Research Divisions and Important Accomplishments

The NCTR Research Divisions work closely in a seamless effort to support FDA's mission to bring safe and efficacious products to the market rapidly and to reduce the risk of adverse health effects from products on the market.

(Click on the links below to navigate to the division or office pages on FDA.gov.)

NCTR Research Divisions and Offices

- **Biochemical Toxicology** — Frederick A. Beland, Ph.D., Division Director
- **Bioinformatics and Biostatistics** — Weida Tong, Ph.D., Division Director
- **Genetic and Molecular Toxicology** — Robert Heflich, Ph.D., Division Director
- **Microbiology** — Carl Cerniglia, Ph.D., Division Director
- **Neurotoxicology** — Sherry Ferguson, Ph.D., Division Director
- **Systems Biology** — William B. Mattes, Ph.D., DABT, Division Director
- **Scientific Coordination** — Bradley J. Schnackenberg, Ph.D., Associate Director

Biochemical Toxicology

National Center for Toxicological Research

About the Division

The Division of Biochemical Toxicology conducts fundamental and applied research designed specifically to define the biological mechanisms of action underlying the toxicity of products regulated by, or of interest to, the FDA. The division's goal is to characterize the toxicities and carcinogenic risks associated with chemicals, specifically those of interest to FDA.

Research within the division is centered on quantifying the toxicities and carcinogenic risks associated with specific chemicals and introducing new risk-assessment techniques to enable regulatory agencies to evaluate the risks associated with exposure to chemicals. The Division of Biochemical Toxicology capitalizes on scientific knowledge in the areas of biochemistry, organic and analytical chemistry, cellular and molecular biology, nutritional biochemistry, toxicology, phototoxicology, computational modeling and simulation-based risk assessment methods, and pharmacology.

Select Accomplishments in 2019

Effect of Carcinogens on Transcriptomic and Epigenetic Alterations in Liver Cells

NCTR scientists investigated the utility of high-throughput microarray gene expression and next-generation sequencing for the in vitro identification of genotoxic and non-genotoxic carcinogens. This approach may substantially enhance the identification and assessment of potential liver carcinogens. The increasing number of man-made chemicals in the environment that may pose a carcinogenic risk highlights the need for developing reliable time- and cost-effective approaches for carcinogen detection and identification. These results have been published in *Food and Chemical Toxicology*.

Epigenome-Wide Association Study of Systemic Lupus Erythematosus (SLE) Based on Ethnicity

NCTR scientists published findings from an epigenome-wide association study of lupus and non-lupus patients, and within those populations examined methylation profiles between African-American and European-American women. In addition, they studied the SLE disease activity status of those individuals — those with less disease (SLE score<6) to those with increased disease (SLE score>6). Different DNA profiles were observed in genes involved in the Type-1 interferon pathway in lupus versus age-matched control subjects. Furthermore, African-American women with lupus had a more robust DNA profile than European women with lupus. The identification of these epigenetic biomarkers can greatly improve the diagnosis of lupus. These results have been published in *Journal of Autoimmunity*.

Scientist Chosen as Advisor at International Agency for Research on Cancer Meetings

Frederick Beland, Ph.D., Director of NCTR's Division of Biochemical Toxicology was selected in 2019 to serve as advisor for the International Agency for Research on Cancer (IARC) meetings. According to its web site, IARC is the specialized cancer research agency of the World Health Organization and is a multidisciplinary research institute with expertise in epidemiology, laboratory sciences, biostatistics, and bioinformatics. Scientists must meet rigorous requirements to be eligible for selection and generally have published significant research related to carcinogenicity of environmental, behavioral, or occupational factors that can increase the risk of human cancer. They may also have expertise in carcinogen testing and/or in carcinogen-hazard evaluation.

Select Research Projects in 2020

- Identification of Mechanistic Biomarkers of Pyrrolizidine Alkaloid-Induced Hepatocarcinogenesis
- Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Patient Outcomes with Triple-Negative Breast Cancer
- Tumor Mutational Signatures of Acrylamide and Glycidamide
- Thermal Inactivation of Staphylococcal Enterotoxins in Milk
- Percutaneous Absorption of the Sunscreen Component Avobenzone
- Development of a Multi-Pathway Physiologically Based Pharmacokinetic (PBPK) Model for Nicotine in Humans
- Animal Models of Pregnancy to Address Medical Countermeasures for Influenza and Chemical, Biological, Radiological, and Nuclear Threats in a "At Risk" Population of Pregnant Women
- Determination of Cytotoxicity and Genotoxicity of Nanomaterials of Interest to the FDA and Mechanism of Action
- Role of Epigenetic Mechanisms in Re-Expression of ER, PR, and HER2 in Triple-Negative Breast Cancer: Effects of FDA Approved Epigenetic Drugs, and Dietary Agents and Nicotine

Bioinformatics & Biostatistics

National Center for Toxicological Research

About the Division

The Division of Bioinformatics and Biostatistics develops integrated bioinformatics and biostatistics capability to address increasing needs of FDA, such as biomarker development, drug safety, drug repositioning, precision medicine, artificial intelligence, rare diseases, endocrine disruptors, and risk assessment. Additionally, the division provides support of NCTR's 1) IT infrastructure and 2) bioinformatics support by analyzing data, managing commercial and in-house soft- ware tools, and conducting training sessions.

1) >50 FTEs, multidisciplinary and diverse
2) Four branches: Bioinformatics, Biostatistics, R2R, and Scientific Computing
3) 40% of staff in research and 60% in support

Select Division Accomplishments in 2019

Breakthrough Therapy Designation (BTD) system

- Text mining study of OND regulatory documents (Meeting Minutes)
- Conducted studies under the ongoing project called Sequencing Quality Control Phase 2 (SEQC2); an NCTR-led consortium effort to assess technical performance and application of emerging technologies for safety evaluation and clinical application. Papers about studies in the following areas are scheduled for submission in 2020:
    1. Cancer genomics using whole genome sequencing
    2. Cancer genomics using target gene sequencing
    3. Reproducibility of whole genome sequencing
    4. Epigenomics
- DILIst, using data from the NCTR-developed Liver Toxicity Knowledge Base, classified about 1,300 drugs known to cause human drug-induced liver injury (DILI).
- Led a CAMDA (Critical Assessment of Massive Data Analysis – platform to evaluate big data analytics using a crowdsourcing challenge mechanism) Challenge for artificial intelligence/ machine learning to predict DILI with genomics data.

Select Research Projects in 2020

Center for Drug Evaluation and Research

- Support DASH (Data Analysis Search Host) Tool
- Develop IND (Investigational New Drug) Smart Template to standardize the IND data submission and management
- Risk Evaluation and Mitigation Strategy (REMS)
- Text Mining Study of Office of New Drugs Regulatory Documents (Meeting Minutes)
- Develop Safety Policy Research Team (SPRT) System

Office of Regulatory Affairs

- Prototyping Automated Laboratory System (ALIS)
- Artificial Intelligence for Food Safety (two projects)

Center for Tobacco Products

- Tobacco Constituents Knowledge Base (TCKB)
- Topic Modeling of Tobacco Documents
- Literature Analysis of Five Major Health Endpoints Associated with Smoking

Genetic & Molecular Toxicology

National Center for Toxicological Research

About the Division

The Division of Genetic and Molecular Toxicology is internationally recognized for its expertise in developing and validating genetic toxicity assays and in interpreting genetic toxicity findings for regulatory decision-making.

Division Research Themes

1) Develop and validate regulatory genetic-toxicology assays
2) Conduct chemical-specific research
3) Develop new paradigms for regulatory decision-making that integrate measures of genetic risk with biomarkers of toxicity by conducting research to develop:
    - Relevant biological models.
    - Comprehensive approaches to monitor genetic variation using technologies such as Next Generation Sequencing.
    - Better ways of evaluating data to determine human risk.

Select Division Accomplishments in 2019

Early Detection

- Developed a minimally invasive gene mutation assay, *Pig-a,* to identify mutagens using a single drop of blood and established an error-corrected next generation sequencing (EC-NGS) to evaluate *Pig-a* mutation in bone marrow erythroid and granulocyte precursors. Find more information in the journal, *Mutation Research.*
- Collaborated with FDA's Center for Devices and Radiological Health to evaluate cancer driver mutations as quantitative biomarkers of cancer risk using EC-NGS and allele-specific competitive blocker PCR (polymerase chain reaction). Find more information in the journal, *Environmental and Molecular Mutagenesis*.
- Developed a rapid, sensitive EC-NGS method for quantifying cancer driver mutations. While easy to perform manually, the method is also suited for robotic handling and batch processing of samples. This facilitates detection and quantitation of carcinogenic biomarkers before tumor formation or in normal- appearing tissue. Find more information in the journal, *Toxicological Sciences*.

Select Research Projects in 2020

- Immunotoxicity Assessment of Nanomaterials Using Human Immune Cell-Based Biomarkers of Innate Immunity
- Somatic Oncomutations as Biomarkers for Translating Preclinical Safety Data to Human Cancer Risk
- Validating the Rat *Pig-A* Assay for Regulatory Use: Determining the Molecular Basis of Mutants Detected in the Rat *Pig-A* Gene Mutation Assay
- Developing an In Vitro System to Evaluate the Disease-Related Toxic Effects of Inhaled Test Agents in Human Airway Tissue Models
- Evaluating the Toxicity and Inflammation Produced By Cigarette Smoke Using Human In Vitro Airway Models
- Developing FDA ddPCR Expertise, Training Opportunities, and the Means to Validate Low-Frequency Oncomutation Measurements
- Advance Safety Assessments of FDA-Regulated Products Using High-Throughput and High-Content Quantitative Approaches in Cultured Human Cells to Evaluate Genotoxicity
- Development and Characterization of In Vitro Testicular Models and Male Reproductive Microphysiological Systems (MPS)

Microbiology

National Center for Toxicological Research

Division Research Themes

The Division of Microbiology scientists engage in research addressing FDA issues with special emphasis on:

- Evaluating the impact of antimicrobial agents, food contaminants, food additives, nanomaterials and FDA-regulated products on the microbiome.
- Developing methods to detect and characterize microbial contaminants in FDA-regulated products.
- Determining antimicrobial resistance and virulence mechanisms of foodborne and other pathogens.
- Conducting research to aid FDA in the areas of women's health, tobacco products, and nanotechnology.
- Improving risk assessments of FDA-regulated products, including the integration of systems biology approaches.

Select Microbiology Accomplishments in 2019

Antimicrobial Resistance and Virulence Mechanisms

- Established a database and an analysis tool to better understand and control Salmonella enterica in foods and feed. Publications available in International Journal of Food Microbiology and Microbiology Resource Announcements.
- Developed and deployed matching algorithms to detect virulence genes from whole-genome sequence data.
- Developed tools to allow the comparison of virulence gene profiles between different Salmonella strains.
- Researched cell plasmids and their role in antimicrobial resistance to determine how plasmids contribute to increased virulence among S. enterica strains. Publications available in Microbial Transposon Mutagenesis and BMC Genomics.
- Demonstrated that antimicrobial exposures an impact plasmid transfer dynamics in a dose-dependent fashion.
- Characterized P. aeruginosa phenotypes when grown with antibiotic-coated catheters in a biofilm reactor and found them to have a higher growth rate, biofilm formation, and cell-invasion potential compared to controls.

Impact of Agents on the Human Microbiome

- Found that higher concentrations of tetracycline and erythromycin could compromise intestinal barrier functions.
- Studied the hypothesis that co-exposure to environmental pollutant, trichloroethylene,

and a high-fat diet would exacerbate the immunotoxicity, gut inflammation, and microbial dysbiosis in offspring. Publications available in Journal of Applied Toxicology and Toxicological Sciences.

- Used next-generation sequencing (NGS) to show commensal organism resistance to Clostridium difficile colonization in an intestinal microbiome cell culture model and to show a reduction in C. difficile toxicity as well as a reduction in inflammation in the presence of certain gut bacteria in an in vivo model.
- Assessed the impact of smokeless tobacco products on members of the oral microbiome.
- Completed a microbiological survey of 85 unopened tattoo and PMU inks, purchased from 13 companies available in the U.S. and almost half (49%) were contaminated with microorganisms, including some species that may be opportunistic pathogens.

Select Research Projects in 2020

- Assessment of the Role that the Microbiome May Play in the Toxicity of Xenobiotics
- Studies on the Intrinsic Structural Multidrug Efflux Pump Mechanisms on Antimicrobial Resistant Salmonella enterica and Their Role in Antimicrobial Resistance
- Detection of Microbial Contaminants in Tattoo inks
- Interaction of Nanoparticles with Gastrointestinal Tract
- Nonclinical Modeling and Risk Assessment of FDA-Regulated Drug-Nanocrystals
- Comparative Study to Evaluate Molecular Assays and Culture-Based Reference Methods for the Detection of Toxigenic *Clostridium difficile* and to Evaluate Storage Conditions on the Recovery of *C. difficile* in Clinical Stool Specimens
- Exploration of Fecal Transplant Mechanisms: Differential Pro-Inflammatory Responses of Intestinal Epithelial and Dendritic Cells to *Clostridium difficile* and Commensal Bacteria
- Multi-Omics Approach to Identify an Antimicrobial Resistance Marker of *Staphylococcus aureus* Associated with Antimicrobial-Coated Medical Devices in a Biofilm Reactor
- Using In Vitro Continuous Culture of the Human Intestinal Microbiota to Evaluate Risk Associated with Bacterial Pathogen Contamination of Fecal Microbiota Transplantation Samples
- Comparative Methods Study for the Detection of *Burkholderia cepacia* Complex from Non-Sterile Pharmaceutical Products
- The Effect of Nanomaterials Used in Dentistry on Biofilm Formation and the Oral Microbiota

Neurotoxicology

National Center for Toxicological Research

About the Division

The Division of Neurotoxicology focuses on increasing FDA's understanding of the processes associated with neurotoxic outcomes—harmful effects associated with the brain and nervous system. This increased knowledge provides FDA with information that may improve risk assessments and new approaches for diagnosis.

Mission

- Identify/quantify neurotoxicity related to FDA-regulated products.
- Develop and validate quantitative biomarkers of neurotoxicity.
- Identify biological pathways of neurotoxicity.

Goals

- Provide the data and expertise necessary for crucial regulatory decisions made by FDA product centers.
- Advance regulatory science research in neurotoxicology for FDA.

Strategies

Develop the following to identify novel markers of neurotoxicity:

- Translationally valid imaging approaches
- Alternative preclinical models
- Cross-species metrics of brain function

Select Neurotoxicology Accomplishments in 2019

Biomarkers of Brain Toxicity

Continuing to validate the use of T_2 mapping via MRI (magnetic resonance imaging) as a more sensitive and specific biomarker of neurotoxicity than ADC (apparent diffusion coefficient) mapping. T_2 relaxation is the speed at which the MRI signal disappears after initial excitation with resonant radio frequency pulse. This speed is dependent on the chemical and physical composition of the sample. In biological systems, T_2 is reproducible in normal conditions and sensitive to changes and appears to provide a higher signal- to-noise ratio, better resolution, and unidirectional changes for the detection and quantification of brain- tissue lesions. In addition, T_2 maps are easier and faster to collect than ADC maps. More information is available in the journal *Neurotoxicology*.

Effects of Anesthetics on Pediatric and Elderly Populations

Evaluated neural stem-cell models to predict the effects of pediatric anesthetics in combination with nitrous oxide. The research data further support the hypothesis that prolonged exposure to anesthesia, early in life, may increase the risk of developing cognitive impairments later in life. Related publications are available in the journal, *Neurotoxicology*.

Select Research Projects in 2020

- Quantifying the Importance of Reactive Oxygen Species (ROS) and Immunomodulation in Drug Effects — In Vivo Studies Using Zebrafish Embryos
- Implementation and Validation of a Rodent Model of Traumatic Brain Injury
- Evaluation of Peripheral Neuropathy as a Functional Biomarker in a Rotenone-induced Rat Model of Parkinson's Disease
- Inveon microPET/CT and its Application to In Vivo Monitoring of Neuronal Apoptosis
- Development and Validation of Interspecies Cognitive Assessments
- Functional Correlates of Gadolinium Deposition in the Rat Brain
- ASK CHILDREN Study — Assess Specific Kinds of Children Challenges for Neurologic Devices
- Using In Vitro Continuous Culture of the Human Intestinal Microbiota to Evaluate Risk Associated with Bacterial Pathogen Contamination of Fecal Microbiota Transplantation Samples
- Utilization of Neural Stem Cell Models and Biomarkers in Assessing the Developmental Neurotoxicity of Pediatric General Anesthetics
- Development of MRI Imaging and Informatics Techniques for Tissue Sampling to Guide and Confirm
- Classical Neuropathology
- Study of Vascular Dysfunction in Brain of Two Transgenic Rodent Models of Alzheimer's Disease (AD): Dietary Impact and Relevance to Human AD
- Evaluation of the Correlation of Ethnicity-related Neuroinflammation Differences in Alzheimer's Disease with ER Stress-induced Endothelial Dysfunction in the Brain
- Evaluating the Contribution of Acute Hypoxia to Models of Early Life General Anesthesia in the Rodent

Systems Biology

National Center for Toxicological Research

About the Division

The Division of Systems Biology's mission is to address problems of food, drug, and medical-product safety using systems biology approaches and innovative technology.

General Themes:

- Translational Safety Biomarkers and Mechanisms
- Alternative Models to Assess Drug Safety
- Technology to Assess Product Safety
- Computational Modeling
- Cross-species Predictions and Translation

Goals:

- Translational prognostic and/or predictive biomarkers for improving pharmaceutical product safety
- Delineated mechanisms for 1) species, tissue, sex, and sub-population specificity in drug toxicity, 2) opioid addiction, and 3) next-generation pharmaceutical toxicity
- In vitro models to evaluate reproductive, developmental, and clinical toxicity
- In silico models for predicting relevant toxicities
- Robust technologies for drug adulteration/compounding

Strategies

- Use as a tool, classes of drugs with known toxicities: such as anthracyclines, tyrosine kinase inhibitors, oligonucleotide therapeutics
- Characterize systems-biology effects with state-of-the-art tools: mRNA and miRNA transcriptomics, epigenomics, metabolomics, proteomics, lipidomics, and imaging
- Integrate data with systems-biology informatics accounting for species, tissue, sex, and sub-population differences
- Incorporate innovative in vitro, computational and instrumental technology e.g. MALDI imaging

Select Systems Biology Accomplishments in 2019

- An Integrated Analysis of Metabolites, Peptides, and Inflammation Biomarkers for Assessment of Preanalytical Variability of Human Plasma. Publication in *J Proteome Res*.
- Use Cases, Best practice and Reporting Standards for Metabolomics in Regulatory Toxicology. *Nat Commun*.
- Evaluation of the Performance of Lipidyzer Platform and Its Application in the Lipidomics Analysis in Mouse Heart and Liver. Publication in *J Proteome Res*.
- Candidate Early Predictive Plasma Protein Markers of Doxorubicin-Induced Chronic Cardiotoxicity in B6C3F1 Mice. Publication in *Toxicol Appl Pharmacol.*

- Testicular Function in Cultured Postnatal Mouse Testis Fragments is Similar To That of Animals During the First wave of Spermatogenesis. Publication in *Birth Defects Res*.
- Determined the Sensitivity of CD-1 and CF-1 Mouse Strains to Morphine and Methadone and Whether Exposure During Gestation Leads to the Development of Neural Tube Defects.
- Investigated the Effects of Opioid Exposure on Neural Precursor Differentiation Using a HumanInduced-Pluripotent Stem Cell Model.
- Employed a Combination of In Vitro (i.e. hiPSCs) and In Vivo Approaches to Investigate the Effects of Opioid Expo- sure on the Developing Neural Tube/Nervous System.

Biomarkers of Doxorubicin-Induced Heart Injury

NCTR scientists developed and used a mouse model of DOX-induced heart injury to identify two proteins (NOTCH1 and vWF) that were elevated in plasma prior to the release of cardiac-specific injury marker, troponin T, in plasma and development of pathology in the heart. Increased level of both proteins was mitigated when toxic effects of DOX were diminished in the heart in mice that received a cardioprotective drug, dexrazoxane, suggesting these proteins as candidate early markers of DOX cardiotoxicity. These early protein markers of DOX-induced heart injury with potential applications in the clinic for monitoring and/or predicting cardiotoxicity induced by DOX will help design more effective treatment regimens. These results have been published in *Toxicology and Applied Pharmacology*.

Development of a Mouse Testis Organ System

The potential for medicines to have adverse effects on male reproductive capacity remains a concern in drug development. While animal tests have been useful, faster methods would be desirable. At the meeting titled “FutureTox IV Progress to Maturity: Predictive Developmental and Reproductive Toxicology for Healthy Children,” scientists from NCTR and CDER presented results of a new in vitro assay where a mouse testis organ system is used to examine the toxicity of chemicals. Further results have been published in *Birth Defects Research*.

Select Research Projects in 2020

- Investigation of the Mechanistic Aspects of Sex-Based Differences in Susceptibility to Doxorubicin-Induced Cardiac Toxicity in Mice
- Predict Tyrosine Kinase Inhibitor (TKI) -Induced Cardiotoxicity Using Induced Pluripotent Stem Cell-Derived Cardio- myocytes
- Verification of Novel Predictive Biomarkers of Doxorubicin-Induced Cardiotoxicity in Breast Cancer Patients
- SpecID for Organic Chemical Characterization
- Molecular Modeling of Opioids and Other Ligands Using a Three-Dimensional Multi-Target Approach
- Matrix-Assisted Laser Desorption Ionization Imaging Mass Spectrometry (MALDI IMS) of Opioids and Subsequent
- Neurotransmitters in Rat Brains
- Evaluation of an In Vitro Mouse Testis Organ Culture System for Assessing Testicular Toxicity

Office of Scientific Coordination

National Center for Toxicological Research

About the Office

The Office of Scientific Coordination provides the professional support necessary to conduct toxicology studies in support of FDA and NCTR's research mission. The support provided to conduct studies includes:

- **Veterinary Services**
- **Microbiological Surveillance**
- **Statistics**
- **Experimental Support**
- **Analytical Chemistry**
- **Nanotechnology Core Facility**
- **Toxicology Support (Pathology, Animal Care, Equipment Maintenance)**

Research and Support Services

Veterinary Services

Veterinary services staff play a key role in the research at NCTR, where they ensure the health and welfare of all animals used in research. The veterinarians participate in the review and monitoring of animal use through the Institutional Animal Care and Use Committee (IACUC). They participate in the research by advising study scientists regarding study design, performing surgery on animals, and monitoring the overall health of the animal program. Veterinary services also includes the microbiology surveillance support staff. This facility has been AAALAC accredited since 1977.

Microbiological Surveillance

Microbiological surveillance staff ensure the animals, environment, food and bedding, and test articles are free from opportunistic pathogens. They are a resource for scientists investigating suspected contaminated cell lines. They support personnel health by microbiological testing of NCTR water and environmental samples.

Statistics

The statistical support staff provides traditional statistical support for the various toxicity studies conducted at NCTR. The services provided include statistical 1) consultation during protocol development, 2) randomization, 3) analysis, and 4) reporting.

Experimental Support

Experimental support staff provide computer- based and in-life support for animal studies. The staff reviews protocols and works with research and support staff to enter study parameters in the animal-data collection system, reviews data, and generates reports at the conclusion of the in-life portion of the study.

Analytical Chemistry

Analytical chemistry research and support are conducted using trained staff and state-of-the- art instrumentation to process a wide range of samples. Test articles and their metabolites are assayed in blood, tissues, or urine to provide measures of exposure. For genotoxic com-pounds, DNA adducts are measured. The high quality of studies at NCTR is ensured by verifi-cation of test-article identity and purity, concen- tration certification and stability of test articles in dosing solutions and vehicles, and the routine surveillance of animal-study materials (bedding, water, and diet).

Animal Care Contract

NCTR maintains an on-site contract for animal care services. The contractor provides trained and proficient staff to perform the tasks necessary for in-life study support including husbandry, environmental enrichment of all animals, formulation and administration of test articles, sample collection, and data collection. The contractor works with the NCTR veterinarians and the IACUC to ensure the health and welfare of the animals.

Nanotechnology

FDA's NCTR and the Office of Regulatory Affairs (ORA) jointly operate and maintain the NCTR/ORA Nanotechnology Core Facility (NanoCore). This core facility is equipped with the appropriate equipment and trained staff to properly characterize and detect nanoscale materials. The NanoCore has been designed to support research investigators with nanomaterial characterization, to develop standard operating procedures for consistent measurement of the nanomaterials, and to develop new procedures to detect nanomaterials in biological matrices in support of toxicology studies in vitro and in vivo.

Pathology Services Contract

NCTR maintains an on-site pathology contract for veterinary pathology and histopathology services. The con- tractor maintains a staff of three veterinary pathologists and a highly trained staff that provide NCTR with services including necropsy, clinical pathology, histopathology slide preparation, rigorous pathology examination, and complete histopathology and pathology reports for each study.

Equipment Maintenance and Repair Contract

NCTR maintains a contract for equipment maintenance and repair that supports the routine preventative maintenance and calibration of equipment, manufacture of minor equipment to support customized research needs, and repair of equipment that is not on a service agreement with the manufacturer.

Thank you!

National Center for Toxicological Research

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To learn more about NCTR, visit

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