Overview of the National Center for Toxicological Research (NCTR)

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NCTR – A Unique FDA Resource

Established in January 1971 by Executive Order as a non-regulatory national resource owned and managed within HHS by FDA to conduct integrated, toxicological research and foster interagency, academic, and industrial collaboration in support of risk-assessment needs related to public health.

NCTR Vision and Mission

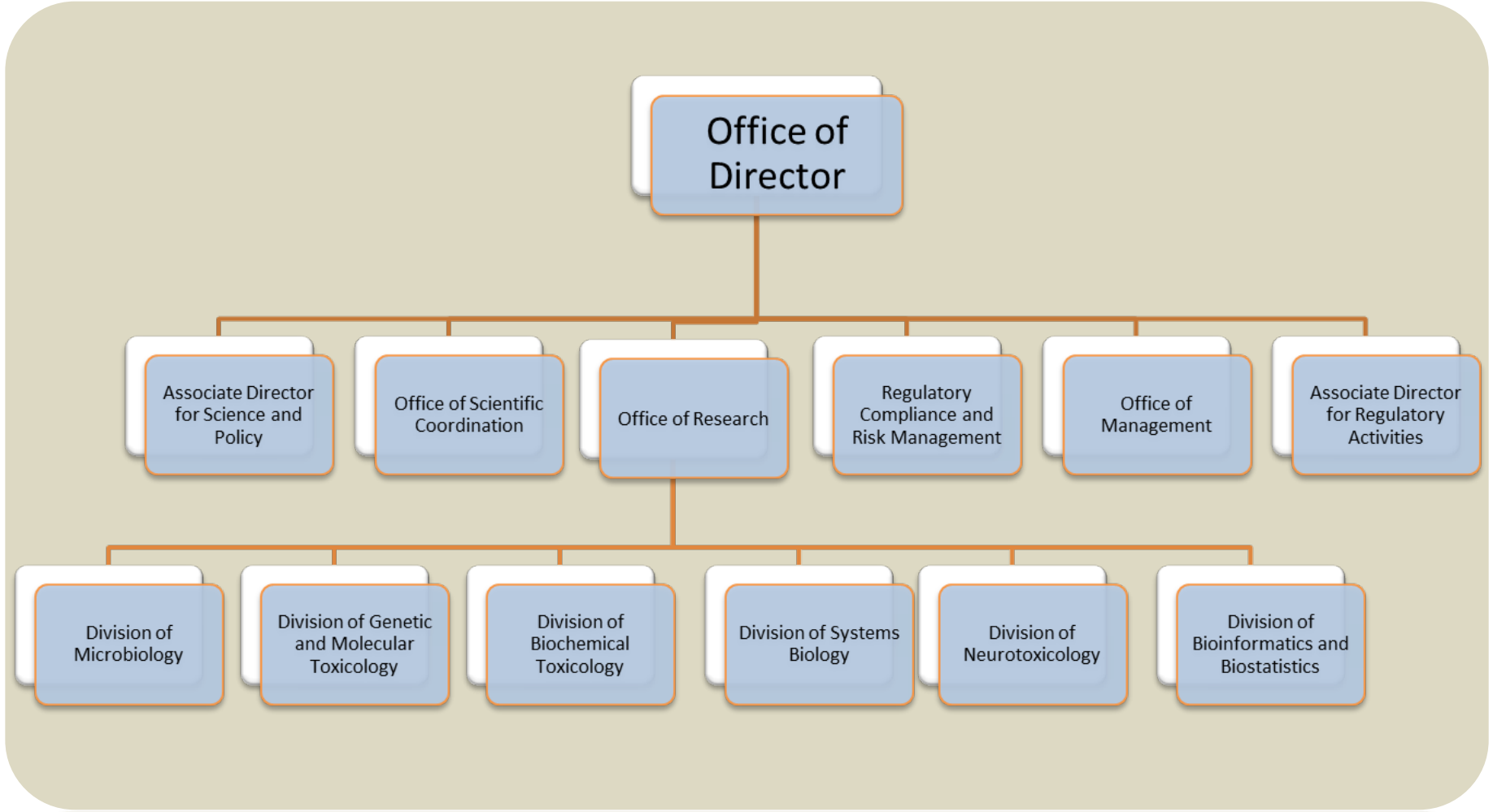
VISION

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

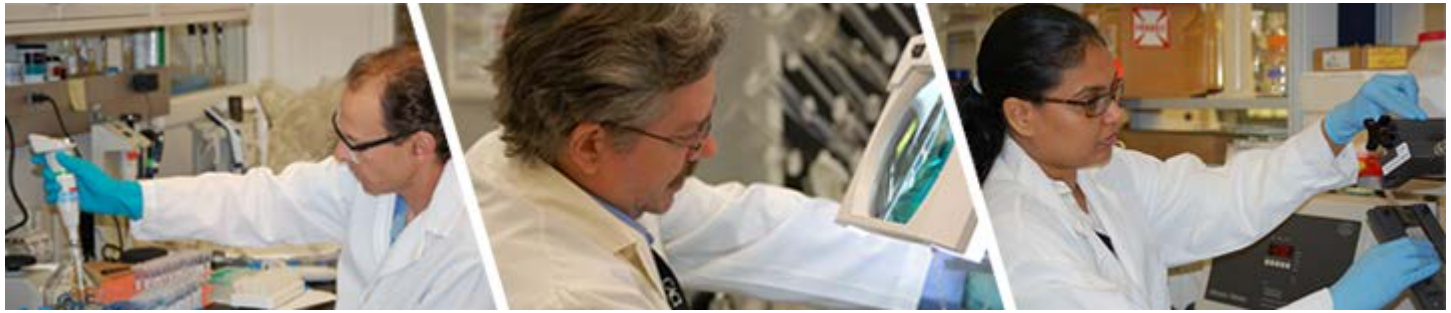
MISSION

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 Organizational Structure



NCTR Staff



Government (FTEs) = 290

Research Scientists = 143

Support Scientists = 65

Administrative = 82

Onsite Contractors = 103

ORISE = 72

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

Top Three Accomplishments in 2017/2018

#1 Improved scientific partnerships within FDA and with external collaborators that provided data for FDA decision making and identified new approaches for assessing safety.

#2 Advanced FDA regulatory science.

#3 Advanced regulatory science research globally.

Accomplishment #1 – Scientific Partnerships

CDER/NCTR

- **Opioids** – Completed method-development study on neural stem-cell growth and differentiation. A larger study to assess prenatal opioid exposure has begun.
- **Pediatric Anesthetics** – CDER and NCTR conducted exposure assessments on desflurane.
- **FDA Warning** – CDER and NCTR research led to FDA warning on 11 pediatric anesthetics.
- **MOU Continues** – Data for monographs on sunscreen ingredients and other non-prescription drugs.

CVM/NCTR

- **Antimicrobial Resistance and the Human Microbiome** – Studied organism diversity and the presence of plasmids that can contribute to antimicrobial resistance.

Accomplishment #1 – Scientific Partnerships continued

OWH/NCTR

- **Precision Medicine –** Studied triple-negative cancers in African-American women.

Public Workshop

- **Sequencing Quality Control-Phase 2 Next Generation Sequencing** in support of the Precision Medicine Initiative.

Accomplishment #1 – Scientific Partnerships continued

CTP/NCTR

Expanded tobacco research capacity – all NCTR divisions are engaged.

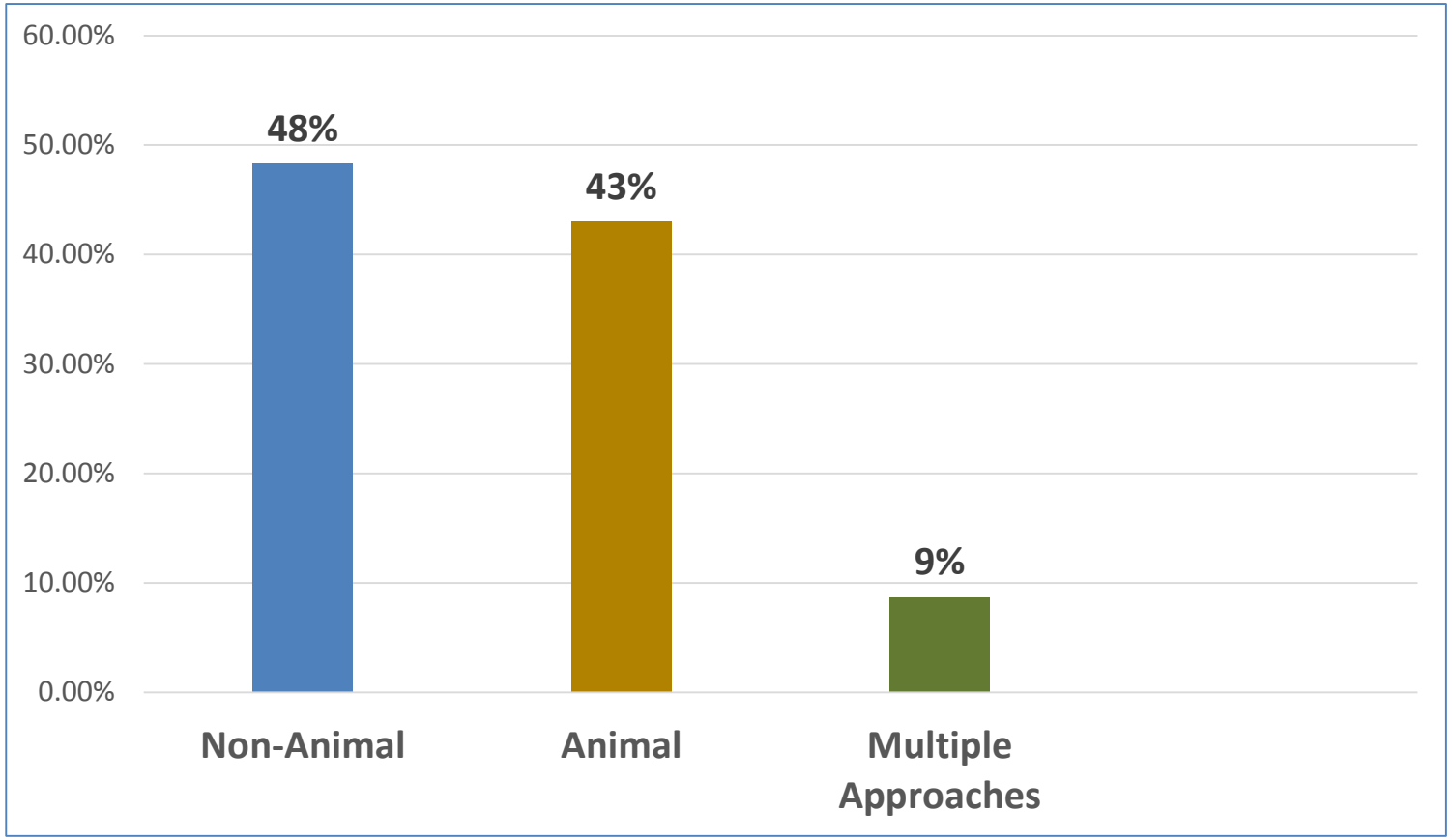
- **Inhalation Toxicology**
  Conduct inhalation toxicology studies of select tobacco product constituents:
  - NNK (pharmacokinetic and subchronic toxicity studies completed)
  - Nicotine (pharmacokinetic study ongoing; subacute study planned)
- **Alternative Models/Toxicology/Adverse Health Consequences**
  Develop and use alternative models (*in vitro 3D* air-liquid-interface (ALI) human airway-cell culture models) to evaluate the toxicity and inflammation produced by whole cigarette smoke.
- **Biomarkers**
  Conduct studies to identify biomarkers of harm using multiple model systems.
- **Modeling/Predictive Toxicology**
  Develop computational tools and models to predict effects of tobacco-product constituents (e.g., physiologically-based pharmacokinetic model for nicotine).
- **Pharmacokinetic Analysis of Nicotine/CTP**
  Conducted in-life phase of a pharmacokinetic study on nicotine in rats; analysis is ongoing.

Accomplishment #1: Scientific Partnerships…continued

FDA/NCTR and NIEHS/NTP Interagency Agreement

- Food contaminants (BPA, Furan, Melamine + Cyanuric Acid, Arsenic studies in developing animals) – **CFSAN** and **CVM**
- A 13-week dosed water study to determine the potential toxicity of aloe in the cecum and large intestine of F-344 rats – **CFSAN**
- Evaluation of brominated vegetable oil in SD rats – **CFSAN**
- Effects of the fibrinolytic enzymes nattokinase and lumbrokinase alone or in combination with aspirin in blood parameters – **CFSAN**
- Two-year dermal carcinogenicity bioassay of triclosan in B6C3F1 mice – **CDER**
- *In vitro* system to evaluate the disease-related toxic effects of inhaled test agents in human airway tissue models – **CDRH** and **NTP**
- Role the microbiome may play in the toxicity of xenobiotics – **NTP**

Projects at NCTR



Non-Animal:
In vitro and *in silico*

Multiple approaches:
Projects using a combination of *in vivo, in vitro,* and/or *in silico*

Accomplishment #2:
Advancing FDA Regulatory Science

Scientific Focus Areas for Expansion:

- Safety Assessment
- Biomarkers
- Bio-Imaging
- 3D Models & Stem cells
- Microbiome
- Precision/Personalized Medicine
- Nanotoxicology
- Inhalation Toxicology
- PK/PD Modeling
- Bioinformatics
- Regulatory Science Training

Accomplishment #2:
Advancing FDA Regulatory Science…continued

Review-to-Research and Return (R2R) Program

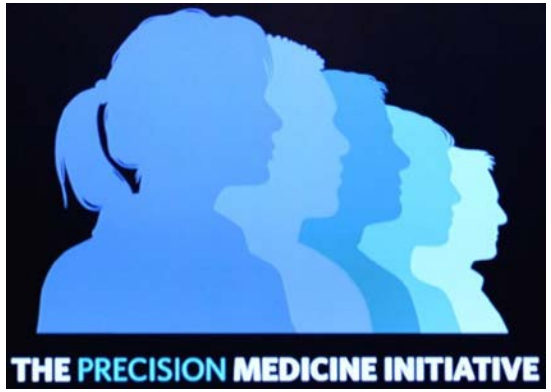
- As a result of NCTR SAB recommendations, created a new Division of Bioinformatics and Biostatistics (DBB) research branch emphasizing the development of the R2R Program.

E*xample projects:*

- Collaborating with CDER/OTS on the DASH system (Data Analysis Host System) to track progression from INDs to NDAs or BLAs and approval of NDAs and BLAs

- Start with upgrading the system and end with the text mining and analysis of its source documents

Accomplishment #2:
Advancing FDA Regulatory Science…continued



Precision Medicine

- Collaborative bioinformatic solutions for Precision Medicine

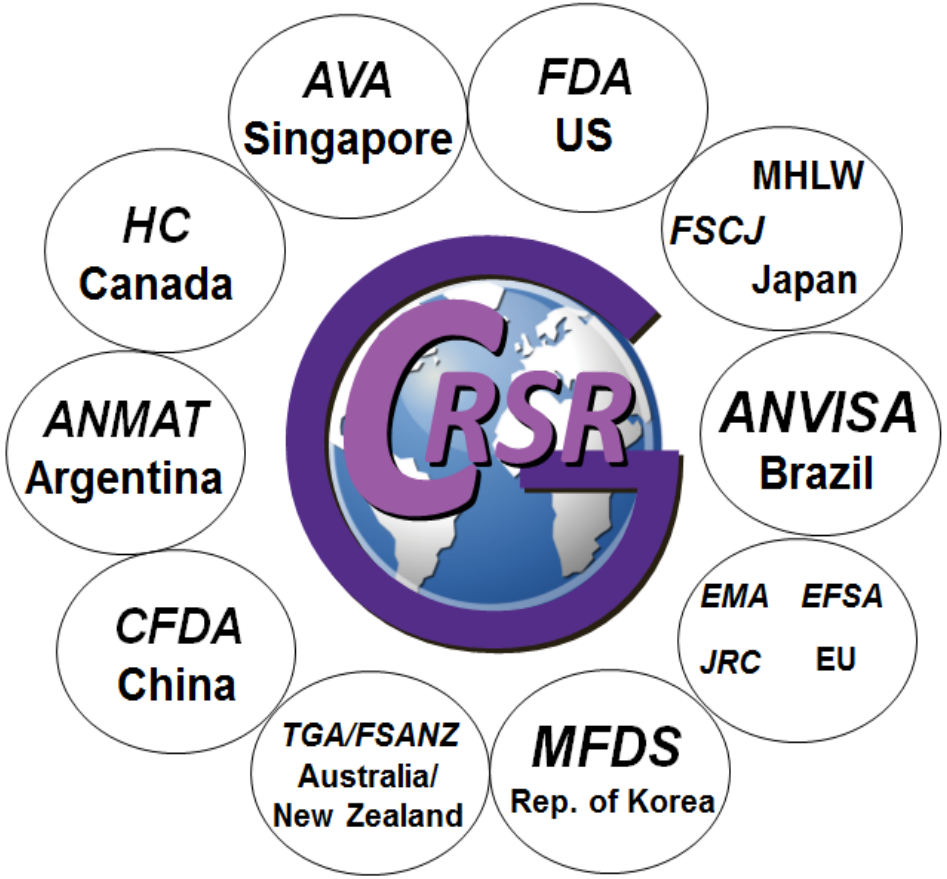
Artificial Intelligence (AI) – Deep Learning Methodologies

- AI is a broad concept of training machines to think and behave like humans. Currently, the DBB is developing deep-learning methodologies to deal with the FDA text documents, such as FDA-approved drug-labeling documents and data from FDA Adverse Events Reporting System (FAERS).

Accomplishment #3:
Advancing regulatory science research globally

Global Coalition for Regulatory Science Research

(Member Countries/Agencies)



Advancing Regulatory Science Research Globally

GSRS 2018

The GCRSR and National Institutes for Food and Drug Control (NIFDC), China co-hosted the Global Summit of Regulatory Science (GSRS18) which focused on **"Risk/Benefit of Dietary Supplements and Herbal Medicine in the Era of Data Science"** on September 25-26, 2018, in Beijing, China with representatives from FDA and about 15 countries.

GSRS 2019

The **9th Global Summit** on Regulatory Science will be held in Ispra, Italy at the Joint Research Centre – European Commission and is tentatively planned for September 16-20, 2019. The topics will focus on "**Nanotechnologies and Nano plastics**."

NCTR Succession Planning

Divisional fine tuning

- Deputy Directors
- Branch Chiefs

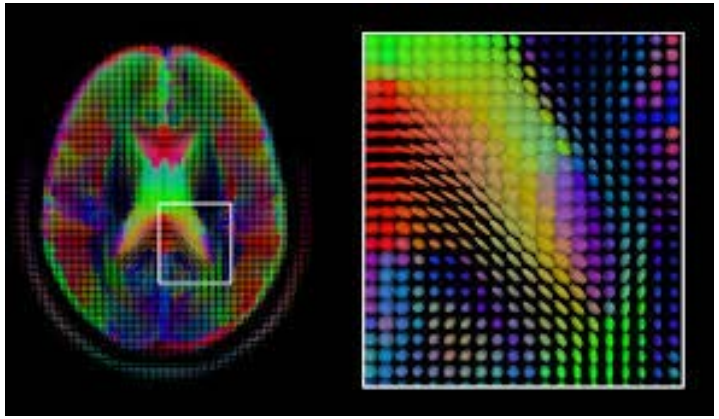
Appointments

- Dr. Tucker Patterson appointed
  Assoc. Director for Science and Policy
- Dr. Rajesh Nayak appointed
  Assoc. Director of Regulatory Compliance and Risk Management
- Dr. Brad Schnackenberg appointed
  Assoc. Director, Office of Scientific Coordination

Transitions

- Division of Bioinformatics and Biostatistics
- Division of Neurotoxicology

New Proposals



Analytics/Imaging Working Group

Perinatal Health Center of Excellence (PHCE)

Why is it beneficial to have a virtual Center of Excellence focused on the perinatal period?

Maternal/fetal pairs represent a unique regulatory responsibility.

Preterm and term-birth neonates and infants represent a vulnerable population that is understudied.

Provides conduit for addressing unmet FDA needs across Centers by creating expert teams and support for needed research across FDA.

Progress of the Perinatal Health Center of Excellence

1

Initial funding has been placed in the FY19 budget request.

2

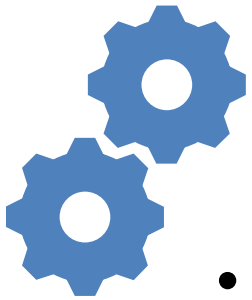
FDA Centers/ORA have **identified liaisons** to manage the development and review of proposals.

3

A **review process** has been jointly established by the Center liaisons.

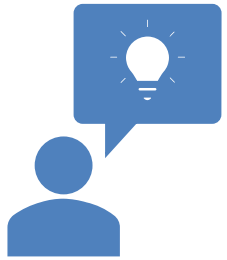
4

15 proposals have been developed for review and consideration for funding.



Approach

- Through coordinated efforts across Centers, prioritized action plans can be created to improve efficiency.
- Skills in areas such as those below are important and can be shared across Centers:
    - cell systems
    - alternate models
    - mathematical modeling
    - laboratory animal studies
    - bioanalytical chemistry
    - information sciences
    - omics
- Collaborative research across Centers, quality science, and mission-focused outcomes are anticipated.



Questions for Discussion

- Can animal models be better utilized for preclinical decision making? What tools would help?
- What are some examples of current regulatory approaches that can be replaced with alternative approaches?
- What alternative models need further evaluation?
- What roles can *in silico* research help?
- Is there a need for additional *in vitro* to *in vivo* extrapolation*?*