Overview of the National Center for Toxicological Research (NCTR)

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NCTR – A Unique FDA Resource

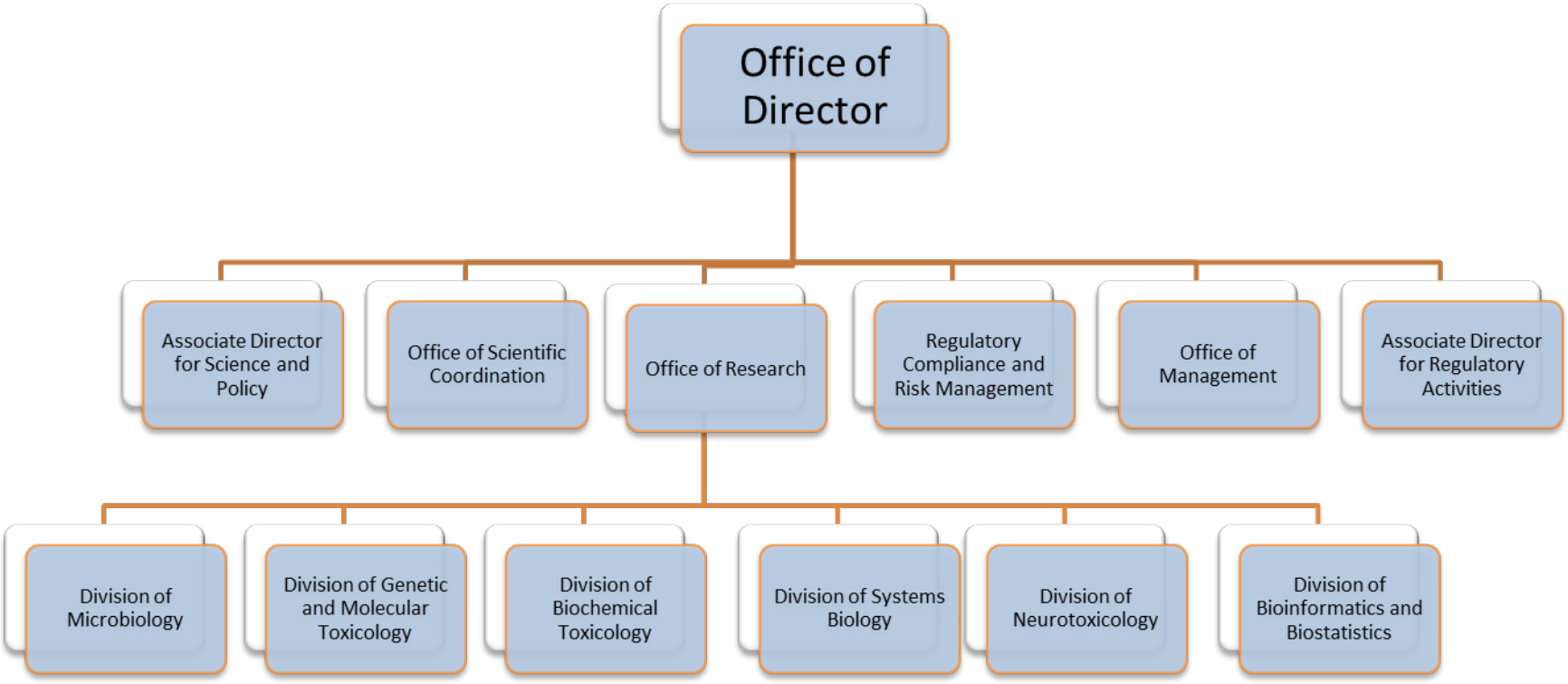
Established in January 1971 by Executive Order as a non-regulatory national resource owned and managed within HHS by FDA to conduct integrated, toxicological research and foster interagency, academic, and industrial collaboration in support of risk-assessment needs related to public health.

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 Positions (Full time employees = FTE)
  - Research Scientists, Staff Fellows & Visiting Scientists : 166 FTE
  - Support Scientists : 45 FTE
  - Administrative : 95 FTE
  - FDA Commissioner Fellows: 2 FTE
- ORISE Post Docs, Graduate Students, Summer Students, etc.: 110
- Onsite Contractors: 250
- **Total NCTR Staff = 668**

NCTR Research Goals

Goal 1: Advance scientific approaches and tools required to support personal and public health

- NCTR objectives align with the priorities outlined in FDA's Advancing Regulatory Science Plan (stimulate and evaluate emerging technologies; develop tools to support precision/personalized medicine). This goal stresses importance of maintaining a strong basic-science core that allows NCTR flexibility to address the ever-changing research needs.

Goal 2: Enhance collaborations with other FDA Centers:

- Generate data in collaboration with the other FDA centers in support of FDA decision making.
- Solicit reviews and collaborators with the concept and protocol review process.
- Build strategic partnerships through virtual centers of excellence.

Goal 3: Promote global interactions in regulatory science:

- Define initiatives that promote NCTR's global activities (research & training) dedicated to building and strengthening the product safety net around the world.

Top Three Accomplishments in 2016/2017

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

Examples of Ongoing FDA Interaction

- **Opioids/CDER**

  Completed a methods-development protocol which enabled NCTR scientists to gain hands-on experience in neural stem-cell growth and differentiation. A larger study to assess prenatal opioid exposure has begun.

- **Pharmacokinetic Analysis of Nicotine/CTP**

  Conducted pharmacokinetic and acute toxicity studies on a tobacco-specific toxicant in rats.

- **Antimicrobial Resistance (AMR) and the Human Microbiome/CVM**

  Studied organism diversity and the presence of plasmids that can contribute to AMR.

- **Pediatric Anesthetics/CDER**

  CDER and NCTR conducted exposure assessments on desflurane.

- **Precision Medicine/OWH**

  Studied triple-negative cancers in African-American women.

Accomplishment #1: Scientific Partnerships

- **NCTR/CDER research in progress to supplement FDA Drug Safety Communication**

  Safety of gadolinium-based contrast agents for MRIs

- **NCTR/CDER research lead to FDA warning** *on 11 pediatric-anesthetic*

- **NCTR Public Workshop**

  Sequencing Quality Control Phase 2 NGS in support of Precision Medicine Initiative

- **MOU with CDER continued**

  Data for monographs on sunscreen ingredients and other non-prescription drugs

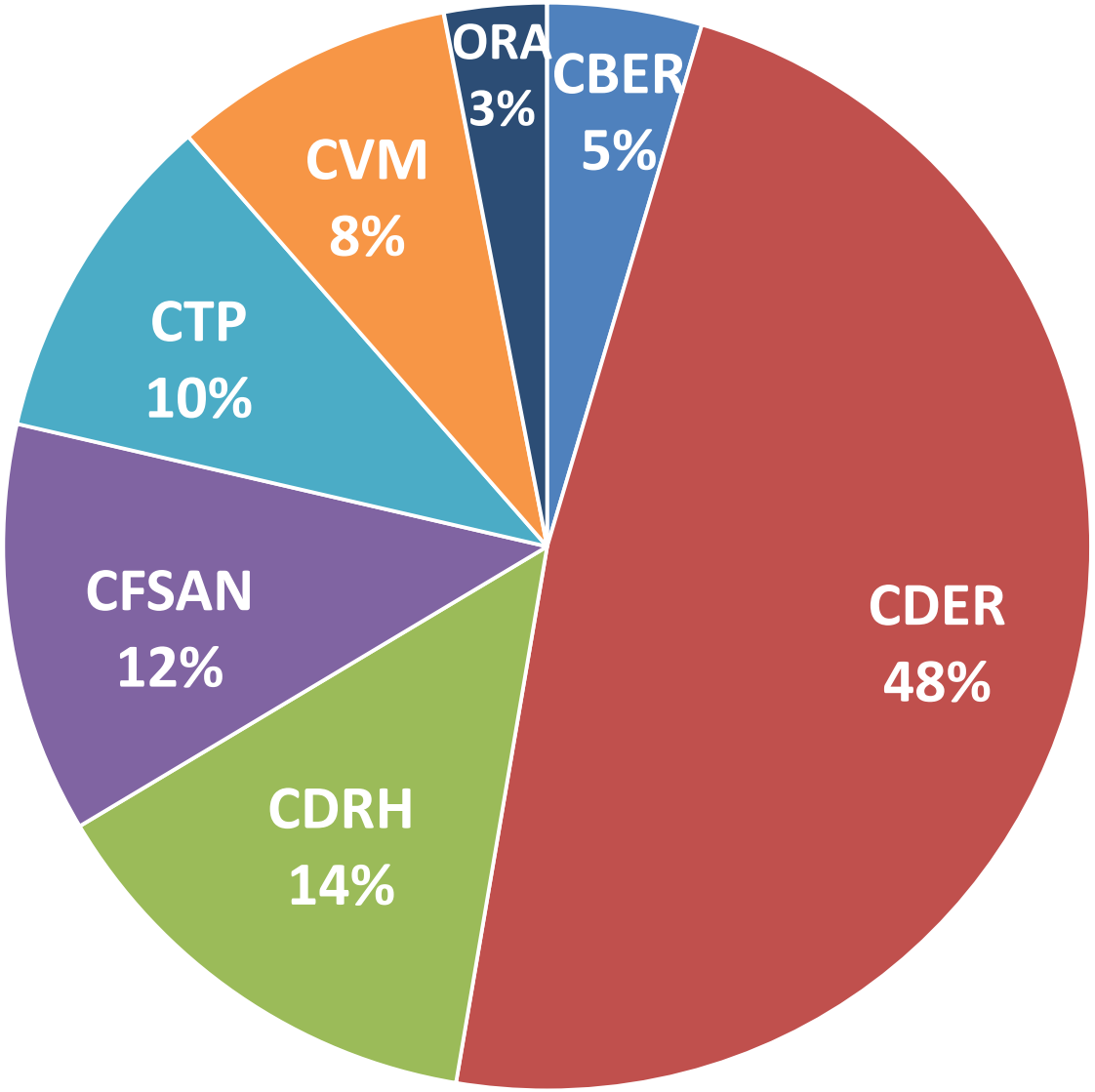
Accomplishment #1: Scientific Partnerships

Expanded Tobacco Research Capacity – All NCTR Divisions are engaged.

- **Addiction**
  - Initiated a self-administration study in rats to address adolescent nicotine exposure as a risk factor for tobacco use in adulthood.
- **Inhalation Toxicology**
  - Completed pharmacokinetic and subchronic inhalation toxicity studies on a tobacco-specific carcinogen (NNK) in rats; final reports in development.
  - Initiated a pharmacokinetic study of nicotine in rats.
- **Alternative Models**
  - Using *in vitro* air-liquid-interface (ALI) human airway models to evaluate the toxicity and inflammation produced by whole cigarette smoke.
- **Bioinformatics**
  - Completed development and transfer of Tobacco Constituent Knowledge Base to CTP.
- **Toxicology/Adverse Health Consequences**
  - Completed the analysis of select smokeless tobacco products for microbial populations and their potential contribution to the development of tobacco-specific nitrosamines (TSNAs).

NCTR Supports FDA Product Centers and ORA

115 of 277 (42%) NCTR Ongoing Projects Are FDA Collaborations



Accomplishment #1: Scientific Partnerships

FDA/NCTR and NIEHS/NTP Interagency Agreement

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

Accomplishment #2:
Advancing FDA Regulatory Science

- 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

- As a result of NCTR SAB recommendations, initiated the creation of a new research branch emphasizing the development of the **R2R (review-to-research and return) Program**.

  Review2Research via data liberation (Example 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

- Focuses on collaborative bioinformatic solutions for **Precision Medicine**

- **Strengthens NCTR-linkages** with FDA product Centers.

Accomplishment #3:
Advancing Regulatory Science Research Globally

- In addition to the 8 countries and the European Union that are members of the Global Coalition for Regulatory Science Research (GCRSR), the Japanese Food Safety Commission (FSCJ), and the National Institute for Food and Drug Control (NIFDC)/ Chinese FDA (CFDA) joined the GCRSR this year.

- The GCRSR and ANVISA, Brasilia co-hosted the Global Summit of Regulatory Science (GSRS17) which focused on **Emerging Technologies for Food and Drug Safety** on September 18-20, 2017 in *DF BRAZIL* with representatives from FDA and over 20 countries.

GLOBAL SUMMIT ON REGULATORY SCIENCE 2017

ANVISA
Agência Nacional de Vigilância Sanitária

Global Coalition for Regulatory Science Research

Succession Planning

- **Divisional fine tuning**
  - — Deputy Directors
  - — Branch Chiefs

- **Transitions:**
  - — Division of Bioinformatics and Biostatistics
  - — Division of Genetic and Molecular Toxicology
  - — Division of Microbiology
  - — Office of Scientific Coordination

New Proposals

- Analytical/Imaging Quantification Group
- Virtual Center on Maternal and Perinatal Medicine/ Developmental Toxicology/Modeling

Why is it beneficial to have a Virtual Center 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.

Why now?

- In the future, the toxicological tools used for human safety assessments will be much different than today.

- Multidisciplinary teams are needed to address the integration of new laboratory methods, *in silico* extrapolation methods, and regulatory actions for FDA-regulated products.

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
- Seeks support via the Reagan-Udall Foundation for FDA, 21st Century Cures, and other sources.

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*?*