Overview of the National Center for Toxicological Research (NCTR)

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NCTR – A Unique FDA Resource

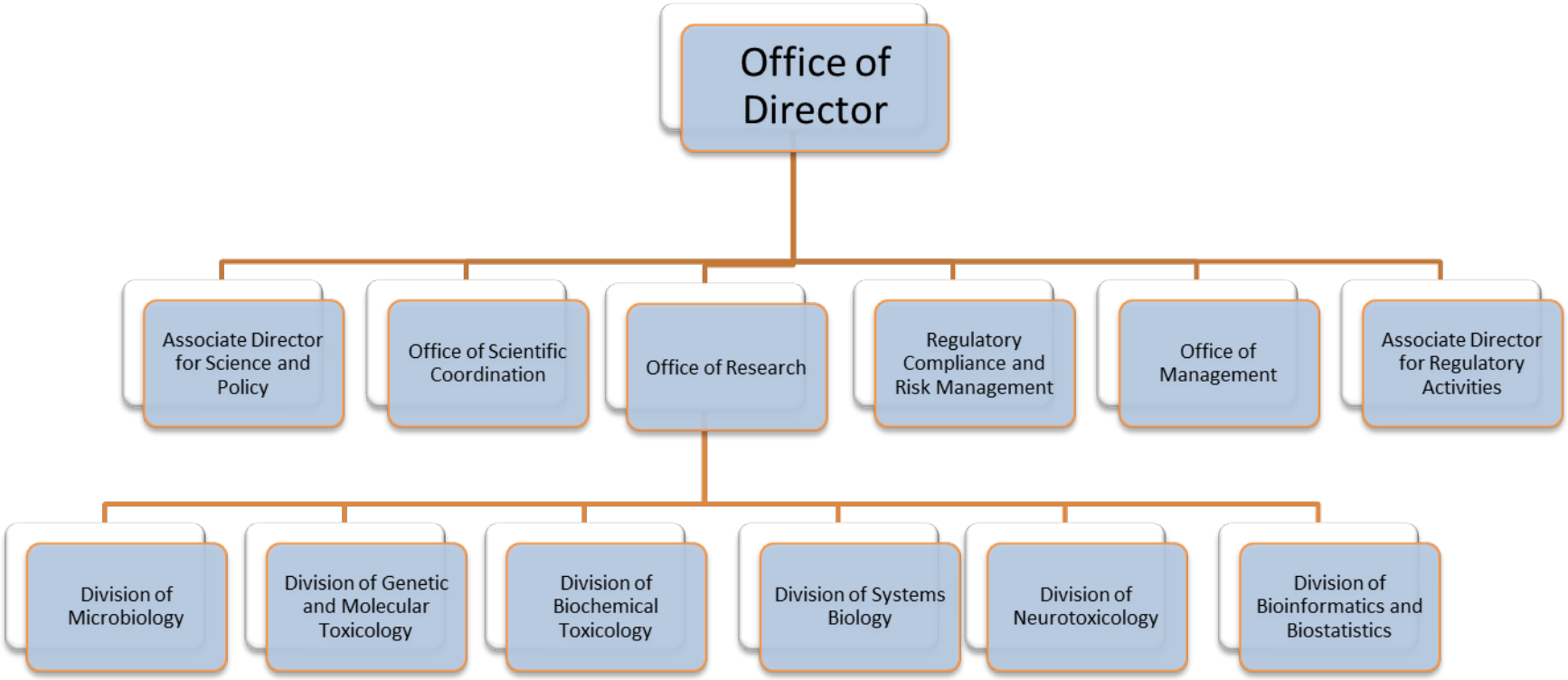
Established in January 1971 by Executive Order as a non-regulatory national resource owned and managed within HHS by FDA to conduct integrated, toxicological research and foster interagency, academic, and industrial collaboration in support of risk-assessment needs related to public health.

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: 4 FTE
- ORISE Post Docs, Graduate Students, Summer Students, etc.: 110
- Onsite Contractors: 250
- **Total NCTR Staff = 670**

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:

- Establish points of contact
- 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.

Accomplishment #1, Part I

Built Scientific Partnerships

Expanded Tobacco Research Capacity — *All NCTR Divisions are engaged*

- **Addiction**

  Initiated self-administration studies in nonhuman primates

- **Inhalation Toxicology**

  Conducted pharmacokinetic and acute toxicity studies on a tobacco specific carcinogen in rats

- **Biomarkers**

  Conducted studies to identify biomarkers of harm using multiple model systems

- **Bioinformatics/Predictive Toxicology**

  Supported CTP's bioinformatics requirements (knowledge bases, enclaves, text/data mining, predictive toxicology, etc.)

- **Toxicology/Adverse Health Consequences**

  Conducted studies to develop methods and alternative models to evaluate tobacco product-associated carcinogenicity, genotoxicity, and microbial contamination

Accomplishment #1, Part II
Built Scientific Partnerships

- **NCTR/CDER studies provide foundation for FDA labeling change**

  Impact of anesthetic exposure during early life in rodents, nonhuman primates, and stem cells

1) NMDA Antagonists:	2) GABA Agonists:	3) Inhalation agents:
Ketamine	Midazolam	Isoflurane
Nitrous oxide	Propofol	Sevoflurane/Desflurane

- **Signed MOU with CDER continued**

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

- **Implemented the R2R framework**

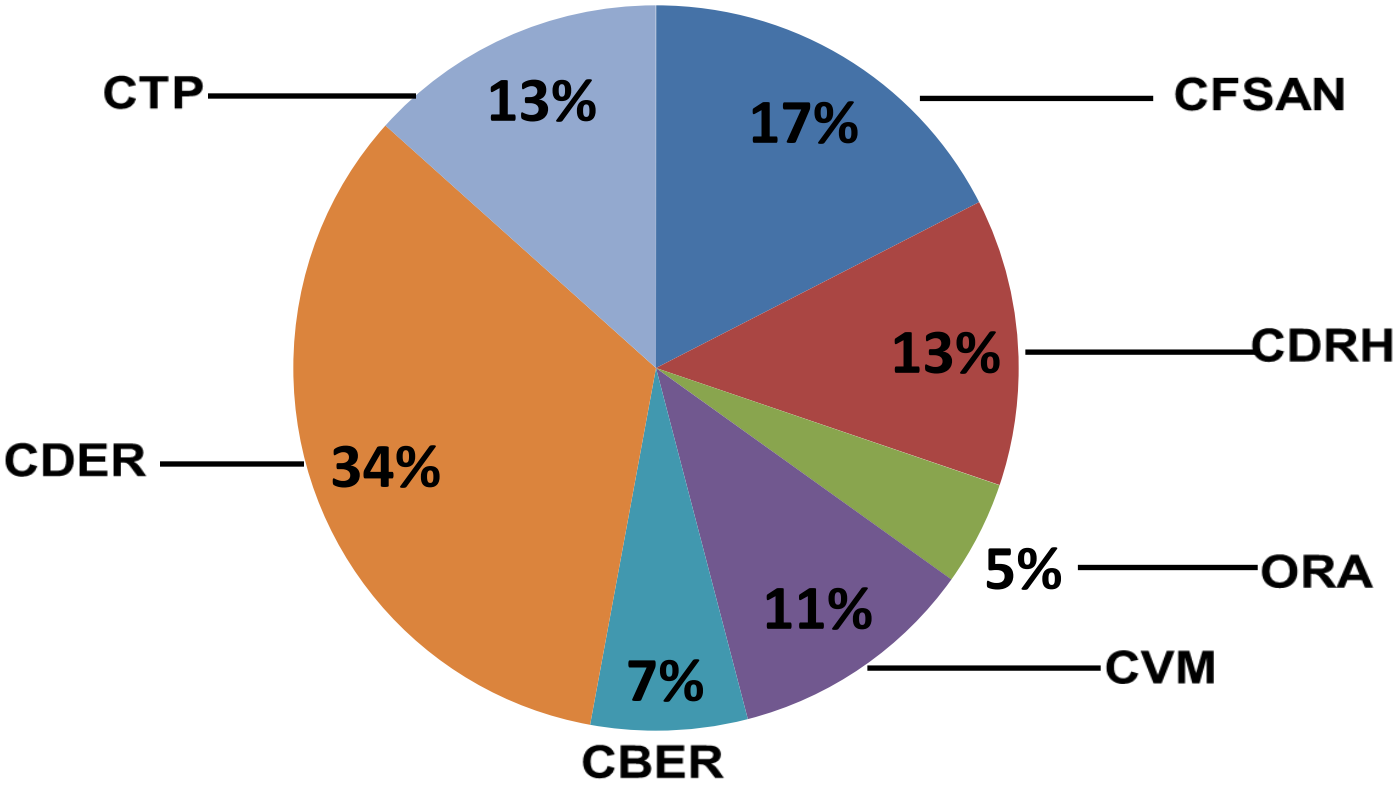
  Research2Review via knowledge uptake

  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

NCTR Supports FDA Product Centers and ORA

172 of 317 (54%) NCTR Ongoing Projects Are FDA Collaborations



Accomplishment #1, Part III

Built Scientific Partnerships

FDA/NCTR and NIEHS/NTP Interagency Agreement

- Food contaminants (Bisphenol A, Furan,, Melamine + Cyanuric Acid, Arsenic studies in developing animals) — CFSAN and CVM
- Topically applied compounds (Retinyl Palmitate, Triclosan) — CDER
- Reproductive and developmental toxicology (Oxybenzone) — CDER
- Medical device and food packaging component (Nanosilver) — CDRH and CFSAN
- Dietary supplements (*Aloe Vera*) — CFSAN
- Initiated PK/modeling studies on developmental exposure to Arsenic — CFSAN
- Verifying new approaches and technologies (microbiome, pharmacokinetic/ pharmacodynamic modeling, 3D cell culture and stem cells, etc.)

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 #3
Enhanced Regulatory Science Research Globally

- Expanded the Global Coalition for Regulatory Science Research (GCRSR) to promote regulatory science. The European Union joined the GCRSR adding over 25 countries to the coalition.

- EFSA co-hosted the 2015 Global Summit on Regulatory Science (GSRS) focused on bioinformatics and its impact on regulatory science on October 12-13, 2015 in Parma, Italy with representatives from FDA and 25 countries.

- The GCRSR Bioinformatics Working Group developed, coordinated and published a summary of the scientific accomplishments for the 5th GSRS.

- The GCRSR Nanotechnology Working Group in conjunction with the FDA Nanotechnology Working Group developed the program for the 6th annual GSRS focused on Nanotechnology Standards and Applications held at NIH with over 150 attendees from 19 different countries.

Top Three Accomplishments in 2015/2016

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

2. Enhanced NCTR organizational and facilities activities to optimize cutting-edge science and collaborative partnerships.

3. Expanded the Global Coalition for Regulatory Science Research (GCRSR), held the 5th and 6th annual Global Summit on Regulatory Science (GSRS), and renewed the Memorandum of Understanding between the FDA and the State of Arkansas.

Succession Planning

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

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

New Proposals

- Analytical/Imaging Quantification Group
- Virtual Center on 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.

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 drugs and chemicals.

Approach

- Through coordinated efforts across Centers, prioritized action plans can be created to improve efficiency.

- Skills in areas such as cell systems, alternate models, mathematical modeling, laboratory animal studies, bioanalytical chemistry, information sciences, and omics are important and can be shared across Centers.

Recent or Ongoing Interactions Between Centers

Pediatric Toxicology (CFSAN and NCTR)

- Wu Y, Fisher J, Neal-Kluever, 2016 Book Chapter, in press, Infant toxicology, "Overview and considerations for the safety assessment of products for infants," *Food Toxicology*.
- Bisphenol A kinetics and PBPK modeling across species

Pediatric PBPK models (CDER and NCTR)

- Duan P, Fisher J and J Wang J. 2016. "Physiologically-Based Pharmacokinetic Prediction of Linezolid and Emtricitabine in Neonates and Infants", in press, *Clinical Pharmacokinetics*.
- Wang J, Avant D, Green D, Seo S, Fisher J, Mulberg A, McCune S, and Burckart G. 2015. A survey of neonatal pharmacokinetic and pharmacodynamic studies in pediatric drug development. *Clin Pharmacol Ther* 98, 328-335.
- Fisher JW, Wang J, George NI, Gearhart JM, and McLanahan ED. 2016. Dietary iodide sufficiency and moderate insufficiency in the lactating mother and nursing infant: A computational perspective. *PLoS One*, Mar 1;11(3):e0149300. doi: 10.1371/journal.pone.0149300.

Ongoing Pediatric Collaborations (continued)

- Methylphenidate extended release PBPK model, X. Yang and J. Fisher, collaborate with John Duan (CDER). Adults, next step is children to understand better generic formulations.

- Critical Path Initiative — 2016: Developing recommendations on renal function assessment and strategies for starting dose selection for term/preterm neonates and infants.

- ILSI-HESI Working group, Nonclinical Models for Neonatal Pediatric Drug Development, (FDA staff from multiple Centers).

Possible Collaborations With Other Agencies

- NIEHS and the National Toxicology Program
- NICHD and the Best Pharmaceuticals for Children Act
- EPA and the National Center for Computational Toxicology

Questions for Discussion

- Can animal models be better utilized for preclinical decision making? What tools would help?
- 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?*