Pregnancy and Lactation Research

Activities, Collaborations, and Opportunities

21st Century Cures Act
Section 2041, PRGLAC Task Force

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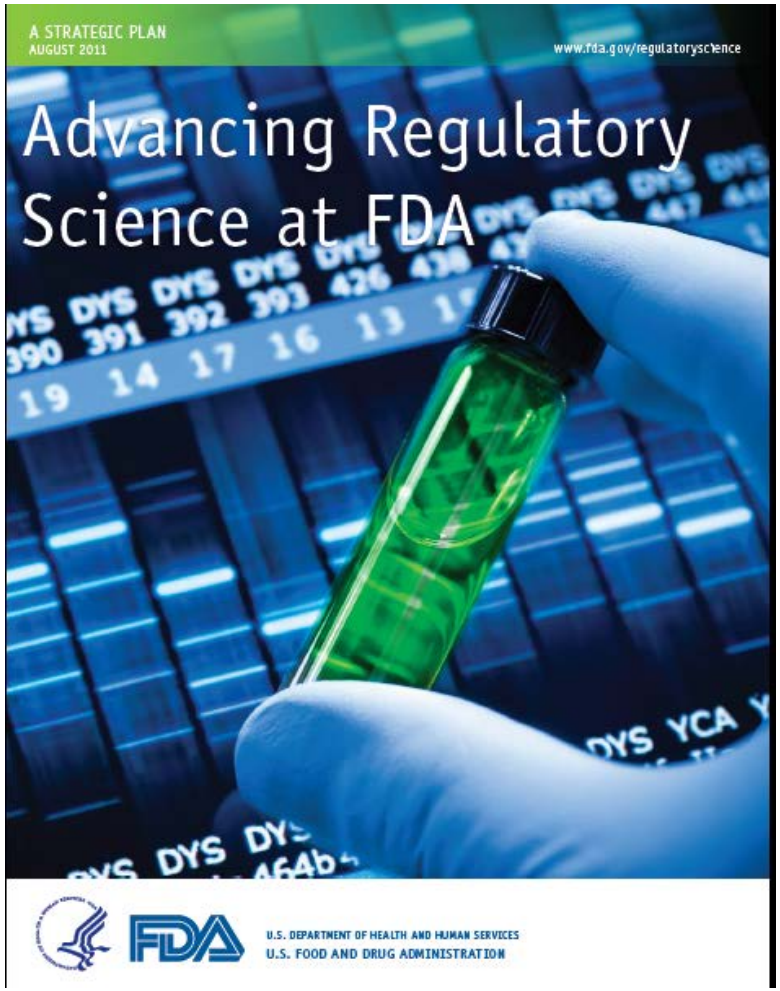
Research Collaborations

FDA collaborates internally and externally with federal, academic and other organizations to develop a variety of programs to benefit pregnant and lactating women

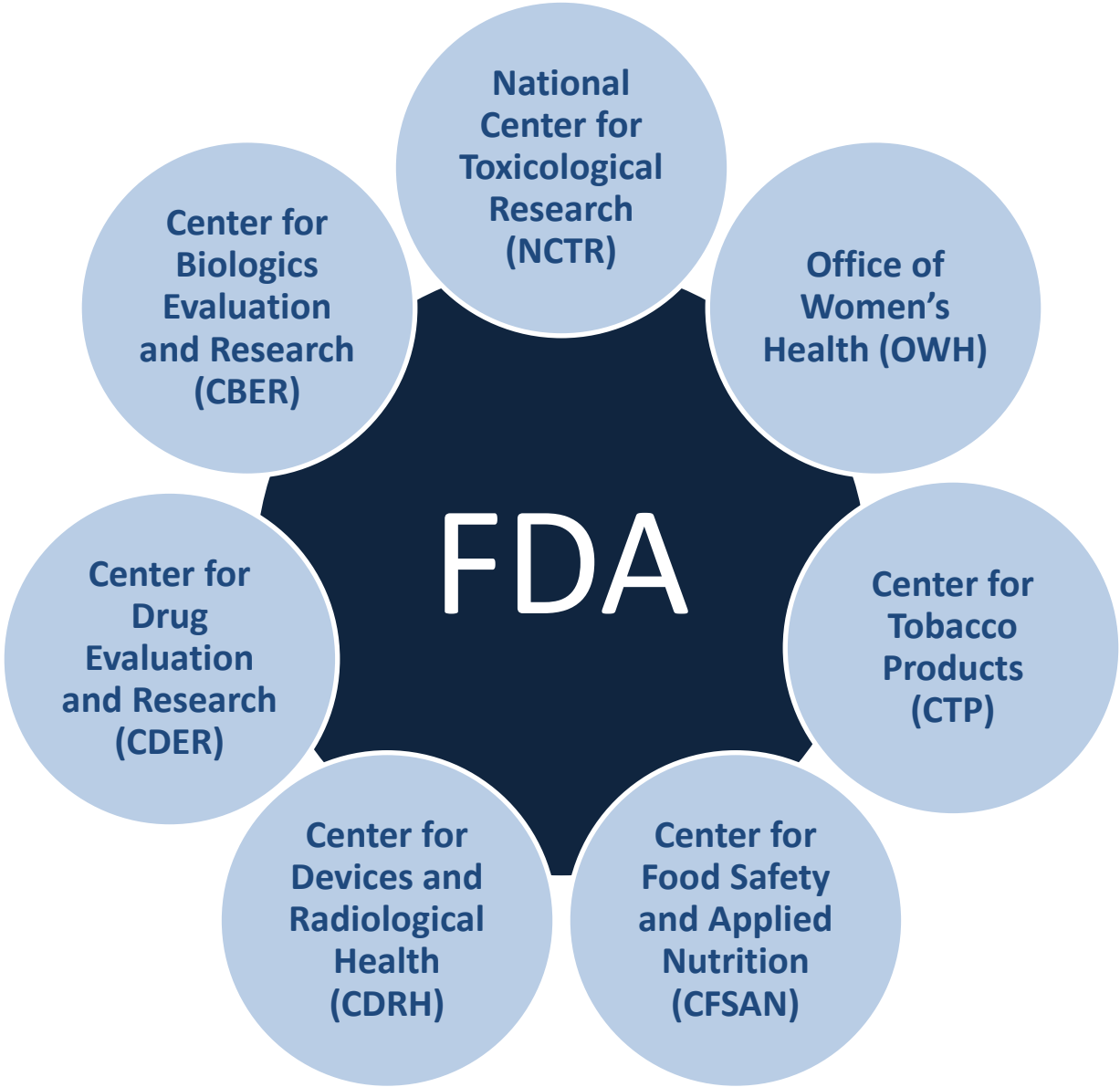
FDA Regulatory Science

What is Regulatory Science?

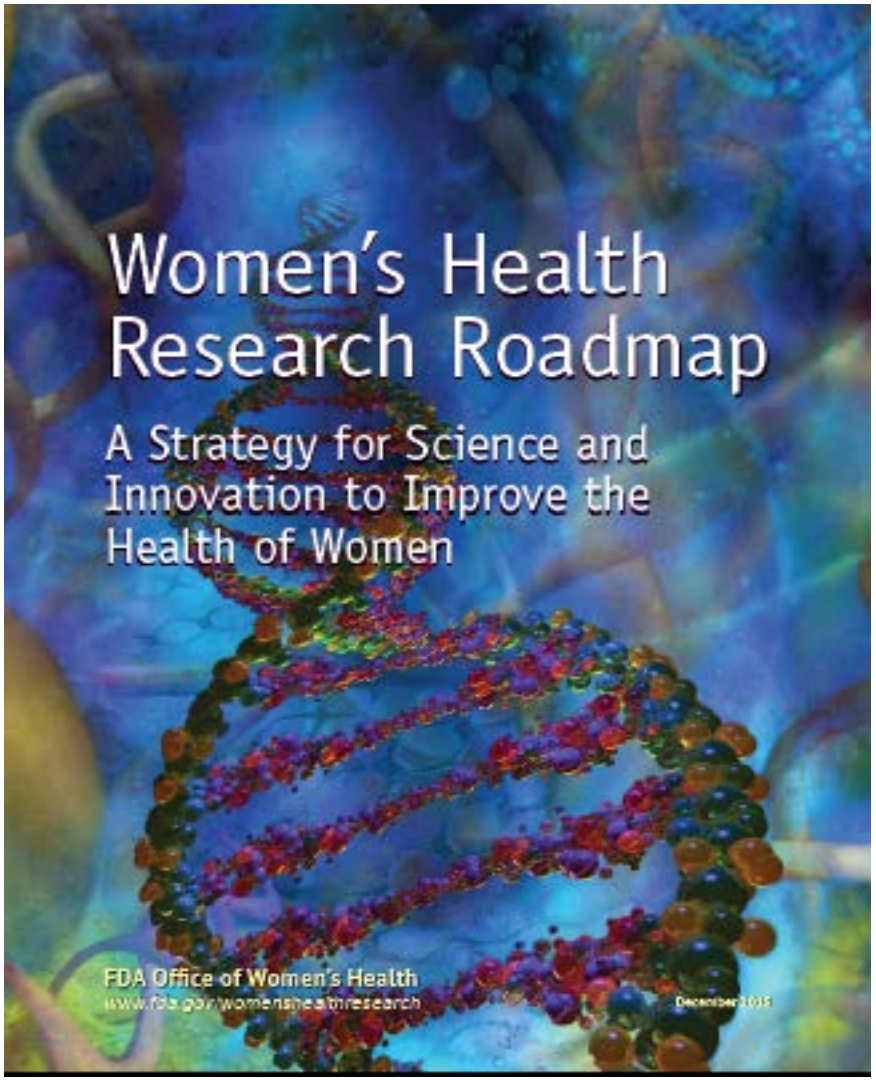
The science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA regulated products.



Pregnancy & Lactation Research



FDA Office of Women's Health



[Women's Health Research Roadmap]

Examples of OWH-Funded Pregnancy and Lactation Research - Intramural

- **Population-based computational framework for assessing xenobiotic disposition and interaction effects in pregnant women**, Annie Lumen, PhD/NCTR (2017)
- **Assessment of Placental Transmission of Zika Virus Glycoprotein E Immunogen**-Evi Struble, PhD/CBER (2016)
- **Bayesian demographic subgroup analyses for pregnant women**- Judy X. Li, PhD/CBER (2015)
- **Evaluation of pharmacokinetics of thrombogenic impurity following different routes of immune globulin administration during pregnancy** - Mikhail Ovanesov, PhD, CBER (2014)
- **Applications of Clinical Pharmacology Principles in Pharmacotherapy of Diseases in Pregnancy** - Srikanth Nallani, Ph.D CDER (2012)
- **MRI in pregnant patients: A systematic analysis of Radio-frequency heating with multi-transmit technology** - Leonardo Angelone, PhD, CDRH (2012)

OWH-Funded Research: Pregnancy (Prevention/Exposure)

Collaborations

Public/Private Collaborations

- Internal Exposure to Drugs and Chemicals[11] (NCTR, CDER, CFSAN, NICHD, Risk Sciences International, Duke University, Proctor and Gamble, University of Rhode Island)
- Medication Exposure Pregnancy Risk Evaluation Program[12] (CDER, HMO Research Network, Kaiser Permanente, Vanderbilt)
- Electromagnetic Exposure Studies[13] (University of Houston, IT'IS Foundation)
- Lactation Studies (CDER, NICHD, Duke)

Interagency Collaborations

- Treating for Two[1,2] (OWH, CDER DPMH, CDC)
- Oxybenzone Studies[3,4,5] (NTP/NIEHS, CDER, NCTR)
- BPA Metabolism[6] (NCTR, CDRH,CFSAN, NTP/NIEHS)
- National Health and Nutrition Examination Survey[7,8] (CFSAN, CDC)
- Dietary Patterns during preconception/pregnancy and Related Disorders and Birth outcomes[9,10] (FDA, USDA)

Medication Exposure Pregnancy Risk Evaluation Program[12]

(CDER, HMO Research Network, Kaiser Permanente, Vanderbilt)

- A collaborative effort intended to provide a large, ethnically and geographically diverse population with which to address a variety of important and timely issues surrounding medication use in pregnancy, and to provide an avenue for ongoing research
- Brings together the clinical and research expertise and population-based databases from 9 study sites which conduct post marketing surveillance studies
- Data resources include information on maternal and infant characteristics and medical care from automated databases

Author Manuscript
Matern Child Health J. Author manuscript; available in PMC 2013 October 01.

Published in final edited form as:
Matern Child Health J. 2012 October ; 16(7): 1349–1354. doi:10.1007/s10995-011-0902-x.

Medication Exposure in Pregnancy Risk Evaluation Program

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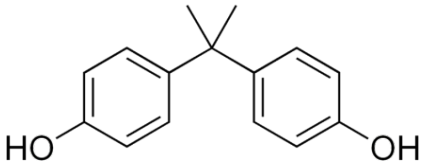
Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP)

- Studies completed using MEPREP, include
  - Birth certificate linkage[14], elective induction[15], linkage algorithms[16], risks of sulfonamide use[17]
  - Evaluation of the prevalence of asthma medications[18], anticonvulsants[19], antidiabetics[20], antipsychotics[21], and antivirals[22]
  - Validity studies to evaluate data elements within the databases and gestational age assumptions based upon administrative data[23,24]
- Ongoing studies using MEPREP, include
  - A 3-year FDA-funded epidemiologic study beginning in 2016, to evaluate the association between neural tube defects and maternal exposure to prescription opioids during early pregnancy

BISPHENOL A (BPA)



- Industrial chemical used in the manufacture of polycarbonate plastic and epoxy resins, possesses weak estrogenic activity
- Found in food and drink packaging, medical devices, dental sealants, digital media (CDs, DVDs), thermal paper products
- Widespread human exposure; detected in ~95% urine samples of US population (NHANES)
- Estimated human daily intake is < 1 µg BPA/kg body weight (bw)
- Major route of human exposure is dietary

CLARITY-BPA

- **Consortium Linking Academic and Regulatory Insights on the Toxicity of BPA**
- **Research consortium involving scientists from:**
  - FDA/NCTR and FDA/Center for Food Safety and Applied Nutrition (CFSAN)
  - NIEHS/NTP and DERT (Division of Extramural Research/Training)
  - 13 NIEHS/DERT-funded university-based grantees
- **Concept was suggested by NIEHS given on-going disagreement on the conclusions on BPA safety of the preponderence of international regulatory agencies, including FDA, and some academic investigators**
- **Intention was to integrate data from university-based grantee studies with those of a guideline-compliant study to contribute to the safety assessment of BPA**

NCTR'S 2-YEAR CHRONIC (CLARITY-BPA "CORE") STUDY

- Modified guideline, GLP-compliant study
- Prior 90-day toxicology study using same model showed clear adverse effects only at 100 and 300 mg/kg body weight/day (Delclos *et al*., Toxicol Sci 139:174-197, 2014)
  - High dose for the 2 year study is 25 mg/kg body weight/day, selected relative to human exposures (i.e. adequate safety margin) rather than 90-study results
- All CLARITY-BPA participants were involved in and agreed upon the final design of the core study
- Detailed descriptions of study concept and design have been published:
  - Schug *et al*., A new approach to synergize academic and guideline-compliant research: the CLARITY-BPA research program. Reprod Toxicol 40: 25-30, 2013
  - Heindel *et al*., NIEHS/FDA CLARITY-BPA research program update. Reprod Toxicol 58: 33-44, 2015

Biomarkers, **E**ndpoint**S** and Other **T**ools BEST (FDA, NIH)

- Clarifies terminology related to biomarkers and surrogate endpoints
- Examples
  - Monitoring Biomarker
    - Serial fundal height during pregnancy (pg 7)
  - Predictive Biomarker
    - Serum protein levels during pregnancy (pg 18)

[BEST (Biomarkers, EndpointS, and other Tools) Resource]
[Clarifying What We Mean When We Talk About Biomarkers]

PREGNANCY REGISTRIES

WWW.FDA.GOV/PREGNANCYREGISTRIES

Pregnancy and Lactation

FDA GUIDANCES

FDA Guidance: Pregnancy and Lactation

- Submission of Premarket Notifications for Magnetic Resonance Diagnostic Devices[25]
- Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components[26]
- **Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications[27]**
- **Reproductive and Developmental Toxicities —Integrating Study Results to Assess Concerns[28]**
- **Evaluating the risks of drug exposure in human pregnancies[29]**
- **Establishing Pregnancy Exposure Registries[30]**

Draft Guidances

- Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format[31]
- Pharmacokinetics in Pregnancy - Study Design, Data Analysis, and Impact on Dosing and Labeling[32]
- Clinical Lactation Studies - Study Design, Data Analysis and Recommendations for Labeling[33]

Opportunities

FDA MECHANISMS FOR EXTERNAL RESEARCH ENGAGEMENT

FDA Centers of Excellence in Regulatory Science and Innovation (CERSI)

Mission & Goals:

To facilitate cooperative relationships and build strategic alliances among FDA and leading **academic institutions** to provide the Agency ready access to research capabilities, training and education and a platform for communication and dialogue with stakeholders in support of FDA's regulatory science needs, scientific workforce development, and its regulatory mission that includes speeding innovations to advance public health.

For more information, visit CERSI web site:
Centers of Excellence in Regulatory Science and Innovation (CERSI)
CERSI Workshops

CERSI Framework

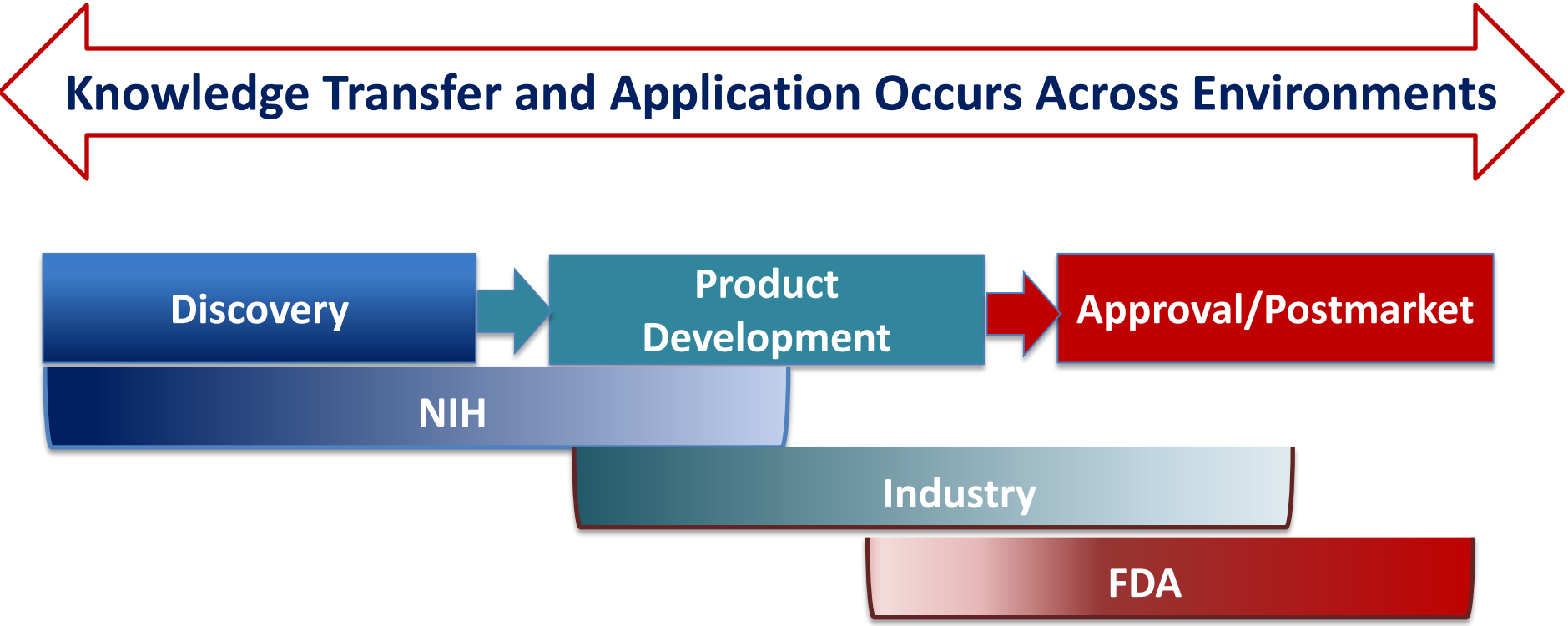
Research	• Research Collaborations with FDA • Pilot Projects
Training	• Certificate & Masters Programs • Scientific Exchange
Administration	• Workshops, Lectures and Visits • Core Facilities and program supports

Extramural Research Funded Through the Broad Agency Announcement (BAA)

- Solicitation encourages science and tech-based participation & academia to meet FDA goals for regulatory science
- Focus on FDA Scientific Priority Areas in *Advancing Regulatory Science*

Regulatory Science Extramural Research and Development Projects

Research Environments



Opportunities to Strengthen Research Collaboration

- **Awareness**
  - Communication
- **Engagement**
  - Relationships
- **Collaboration**
  - Actively working together
- **Dissemination**
  - Strategic outreach
- **Endurance**
  - Continued Collaboration

THANK YOU

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