Center for Drug Evaluation and Research (CDER) Perspective

National Center for Toxicological Research (NCTR) Scientific Advisory Board

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CDER-Office of New Drugs Pharm/Tox Staff: Role in Regulatory Drug Development

NCTR Science Advisory Board

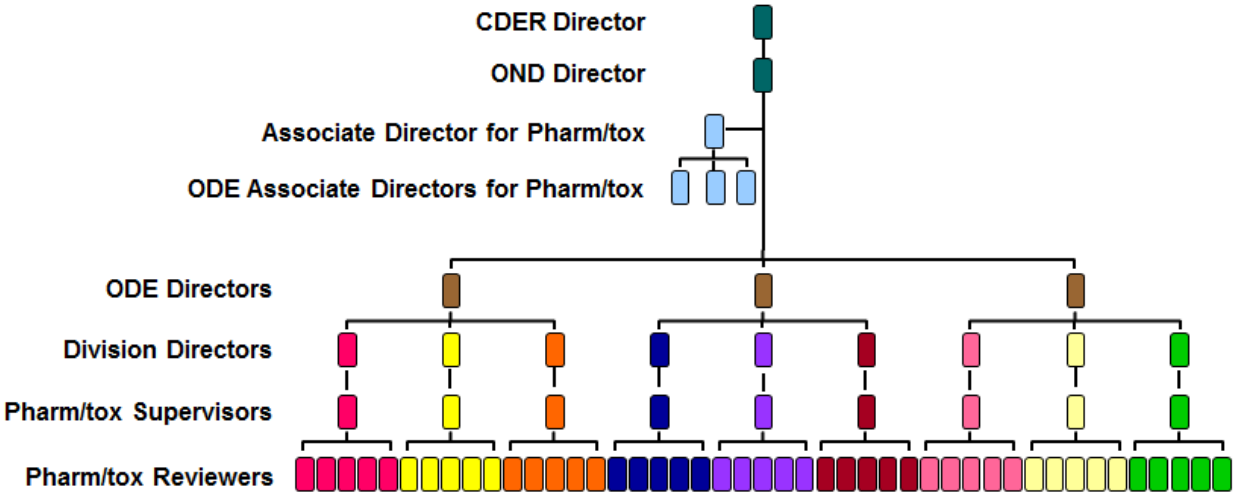
November 2016

Tim McGovern, PhD

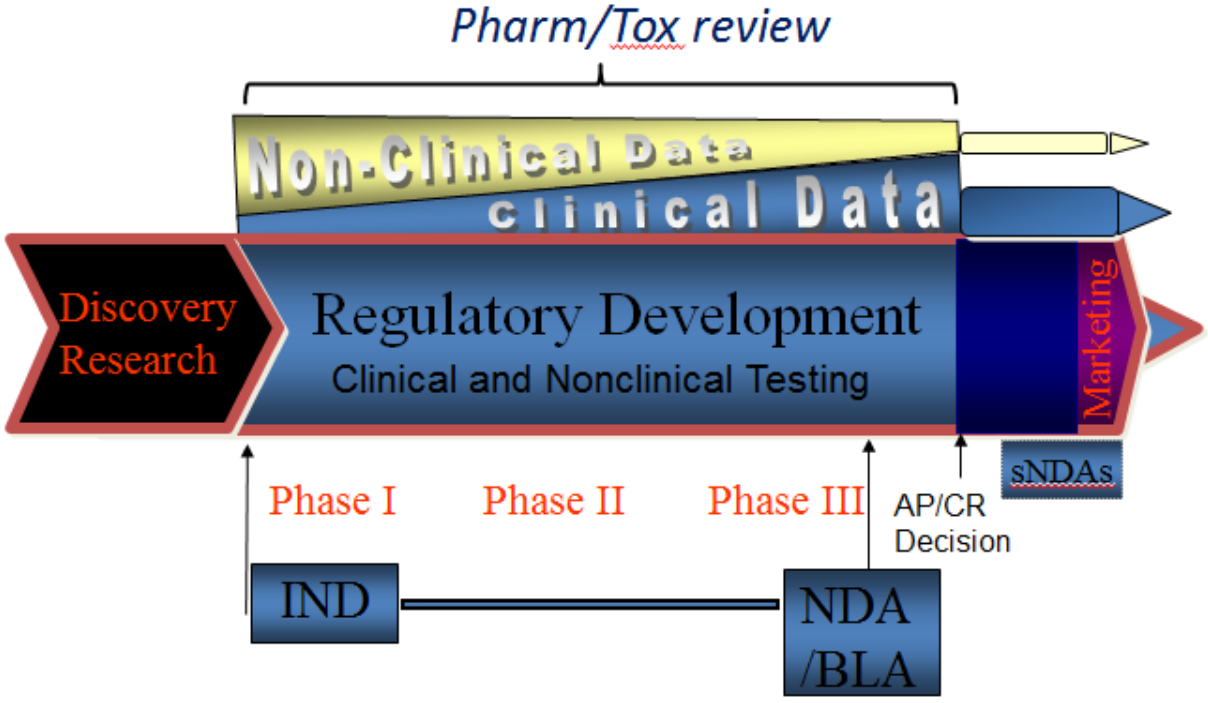
ODE Associate Director, Pharmacology/Toxicology

Office of New Drugs, CDER, FDA

CDER Organizational Chart (focus on pharm/tox group)



OND Pharm/Tox:
Place in Regulatory Drug Development



Use of Pharm/Tox data

- Identify reasonably safe dose range to explore in clinical trials
- Identify clinical monitoring needed beyond ‘standard’ safety assessments
- Identify or predict risks that are not captured in human trials

(e.g., carcinogenicity, teratogenicity)

What is the intent and use of pharm/tox in NEW drug development?

- Establish pharmacological properties of compound

- Understand toxicological profile
  (target organs, exposure/response, reversibility)

Is submitted data sufficient to conclude that proposed clinical investigation is reasonably safe?

Scope of “complete” Pharm/Tox information

- Pharmacology
  - o Cellular & Molecular mechanism of action, Specificity
  - o ‘Proof of Concept’ in vitro/in vivo studies
  - o Safety Pharmacology (CNS, Respiratory, Cardiovascular

- Pharmacokinetics

  ADME: Absorption, Distribution, Metabolism, & Excretion

  - o From animal species & human metabolism

- General Toxicology
  - o Two species, 1 rodent, 1 non-rodent
  - o In-life & necropsy evaluations
  - o Acute & chronic administration of drug + recovery periods

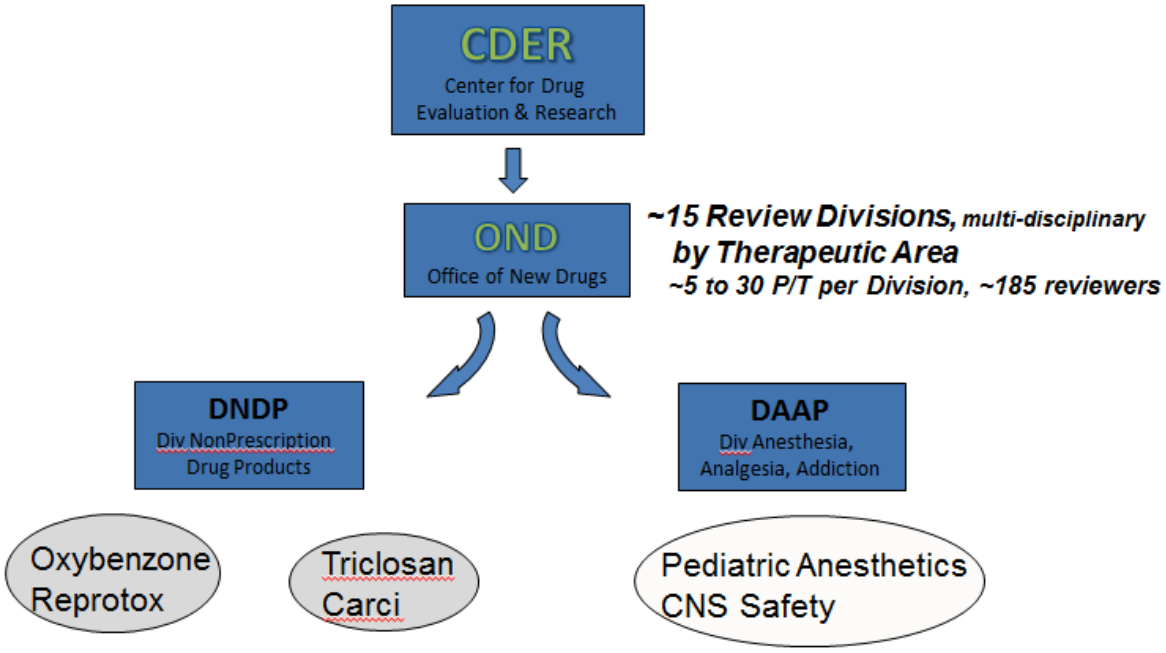
Scope of “complete” Pharm/Tox information

- Genetic Toxicology
  - In vitro & in vivo assessments
- Carcinogenicity
  - e.g., from weight-of-evidence paper to 2 yr rodent studies
- Reproductive Toxicology
  - Fertility
  - Teratogenicity & embryofetal development
  - Peri- & post-natal development
- *Product specific assessments*
  - e.g., Juvenile animal studies, pancreatic safety studies, etc…

Complete pharm/tox information not expected immediately

- Timing depends on scope of proposed clinical trial & type of product
  - ICH M3(R2): Small molecules
  - ICH S6: Biologics
  - ICH S9: Anti-Cancer Pharmaceuticals
- All pharm/tox topics considered important safety issues
- Expectation is that all nonclinical topics be addressed, appropriate for the scope of the clinical program

CDER/OND Pharm/Tox & NCTR Connections: Examples



Pharm/Tox & NCTR Connections

- ~ 70 current CDER-NCTR collaborations
- Some current collaborations include:
  - *Assess critical gaps in safety assessment* of widely used and/or widely available drug substances
    - Increasingly important collaboration with innovations to Nonprescription Drug Products monograph review process
      - *Laboratory research; Review of submissions*
  - *Serve as co-PI on various projects including research on*
    - *drug-induced cardiotoxicity*
    - *Genotoxicity*
  - *On-site laboratory training in neurotoxicity methods*

Potential collaboration on nonclinical programs for NEW drug approvals?

How do we better extrapolate relevance of nonclinical toxicology findings to humans, and translate those findings to human risk?

- Genetic toxicology
- Carcinogenicity
- Reproduction & Development

How do we better identify and evaluate alternatives/ refinements to current testing strategies intended to improve prediction of human risk?

- In vitro developmental assays (e.g. mEST, zebrafish)
- Microphysiological approaches (tissue/organ/human on a chip)

Applied Regulatory Science, Clinical Pharmacology and Translational Sciences Perspective

NCTR Science Advisory Board

November 2016

David Strauss, MD, PhD

Director, Division of Applied Regulatory Science (Acting)

Senior Advisor, Translational & Experimental Medicine

Office of Clinical Pharmacology, Office of Translational Sciences

Center for Drug Evaluation and Research

What We Do …

- **Office of Translational Sciences**
  - Promote innovation in drug regulatory review
  - Assure the validity of clinical trial design and analysis
  - Develop and apply quantitative approaches
  - Promote scientific collaboration
  - Ensure alignment of CDER research with CDER goals

- **Office of Clinical Pharmacology**
  - Evaluate pharmacokinetics and pharmacodynamics
  - Understand inter-patient variabilities
  - Optimize dose and dose regimen to balance benefit and risk
  - Conduct research to advance clinical pharmacology and better evaluate benefit and risk

Division of Applied Regulatory Science (DARS)

Vision

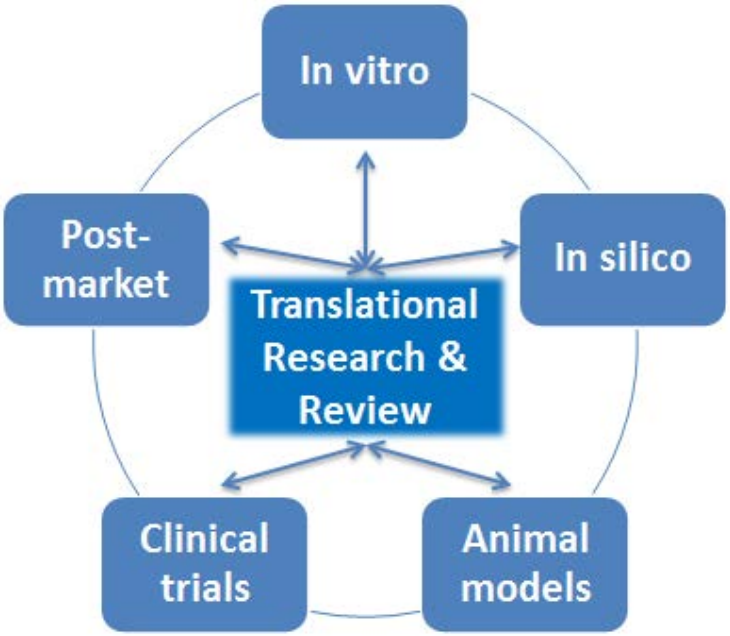
- To move new science into the CDER review process and close the gap between scientific innovation and product review

What does DARS do?

- Perform mission-critical applied research to develop and evaluate tools, standards and approaches to assess the safety, efficacy, quality and performance of drugs
- Perform expert regulatory review consultations for immediate regulatory needs, such as mechanistic evaluation and biological plausibility of new safety signals

DARS Priorities

- **Translational regulatory science**
- **Collaboration and interdisciplinary team approaches**
- **Implementation of new regulatory review methods and programs**



Broad, multidisciplinary expertise:

- Pharmacologists, toxicologists, physiologists, pharmacokineticists
- Physicians, veterinarians, pharmacists
- Immunologists, microbiologists, molecular/cell biologists
- Biochemists, inorganic chemists, pharmaceutical scientists
- Computational biologists, engineers, bio-physicists, mathematicians

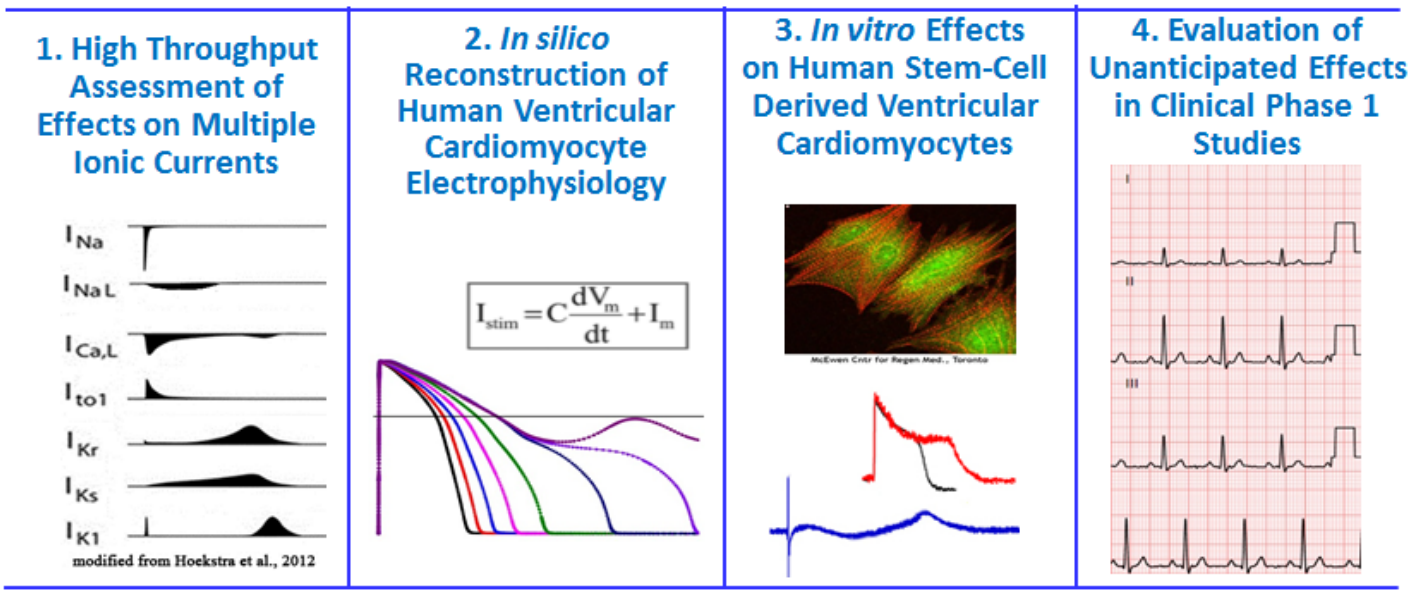
Highlighted Applied Research and Regulatory Review Areas

1. Modernizing toxicology/safety pharmacology with humanized assays and genomics
    - Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative
    - Humanized mouse models (immune and liver)
    - Genomic (microRNA) biomarkers for tissue injury

2. Bioanalytical, pharmacokinetics and drug-drug interactions

3. Informatics tools for mechanistic safety and regulatory review consults
    - Chemical informatics
    - Biomedical informatics
    - Mechanistic safety and pharmacology consults

Comprehensive *in vitro* Proarrythmia Assay (CiPA): Four Components



Goal: Develop a new in vitro paradigm for cardiac safety evaluation of new drugs that provides a more accurate and comprehensive mechanistic-based assessment of proarrhythmic potential

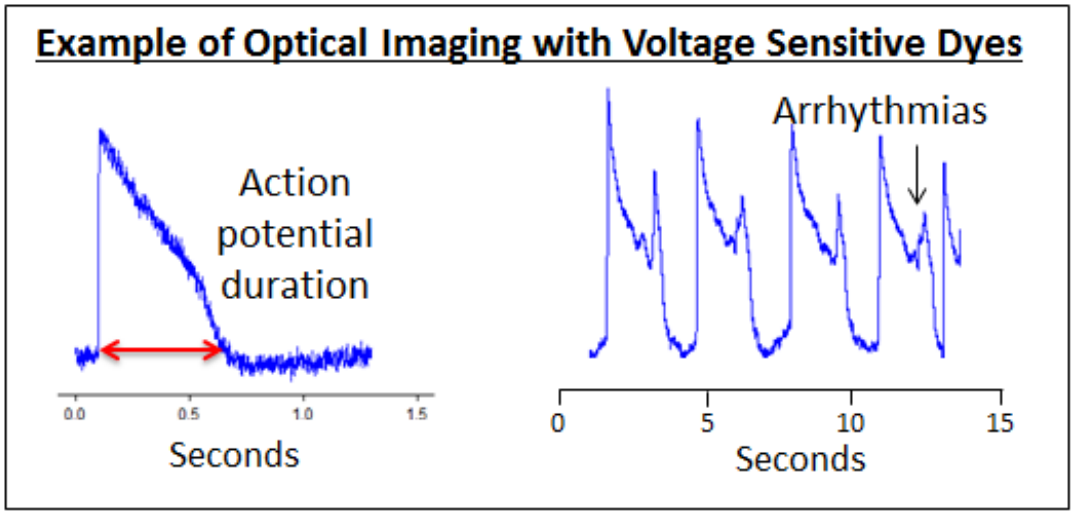
- DARS is leading applied research across all four components to develop and validate this novel regulatory paradigm in collaboration with all major global drug regulatory agencies, multiple public-private partnerships, industry and academia

CDER-CDRH-NCTR Collaboration

Comprehensive Translational Assessment of Human Induced Pluripotent Stem Cell Derived Cardiomyocytes for Evaluating Drug-Induced Arrhythmias

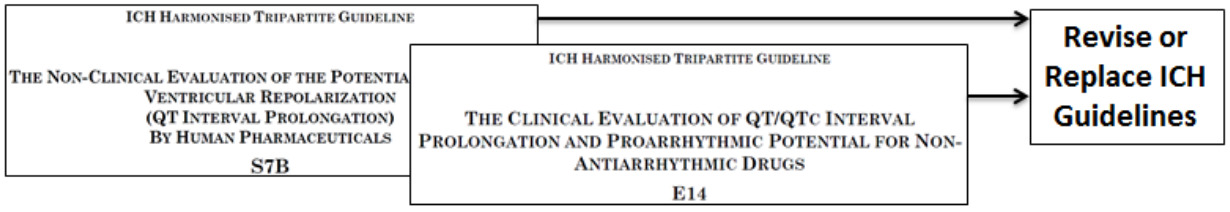
Ksenia Blinova, Jayna Stohlman, Jose Vicente, Dulciana Chan, Lars Johannesen, Maria P. Hortigon-Vinagre, Victor Zamora, Godfrey Smith, William J. Crumb, Li Pang, Beverly Lyn-Cook, James Ross, Mathew Brock, Stacie Chvatal, Daniel Millard, Loriano Galeotti, Norman Stockbridge, David G. Strauss

Toxicological Sciences (2016) in press - doi: 10.1093/toxsci/kfw200

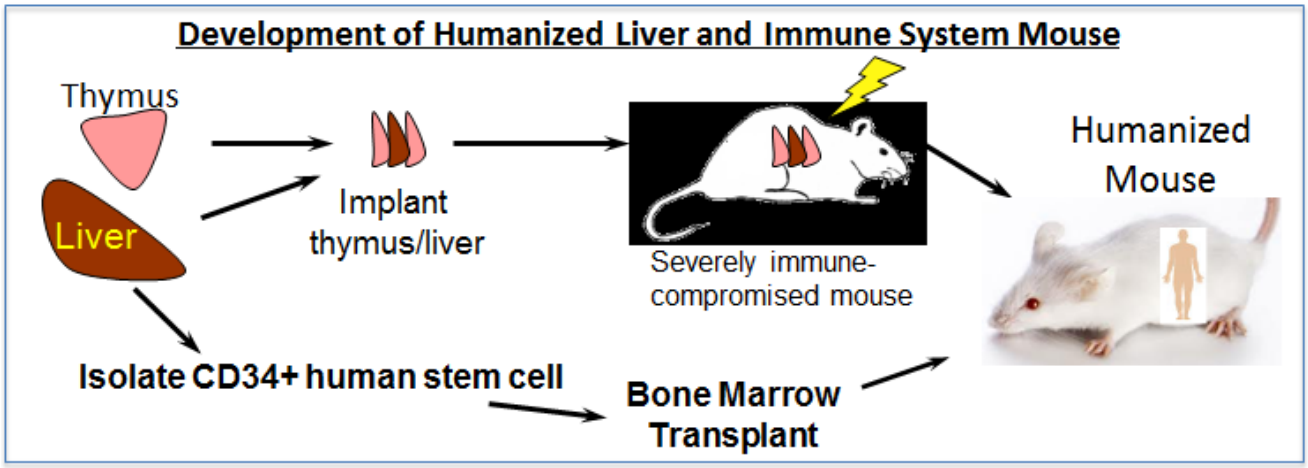


CiPA Progress & Expected Outcomes

- Standardized, mechanistic-based studies that can be applied early in drug development to aid in compound selection
- Drugs that may be dropped from development under current paradigm could have a clearer path to advance
- QT prolonging drugs on the market that are not proarrhythmic could have labeling updated to reflect this
- Model for mechanistic-based approaches to be applied to other drug safety areas
- Qualification studies to be completed and presented to International Conference on Harmonization (ICH) by December 2017



Humanized Mouse Models

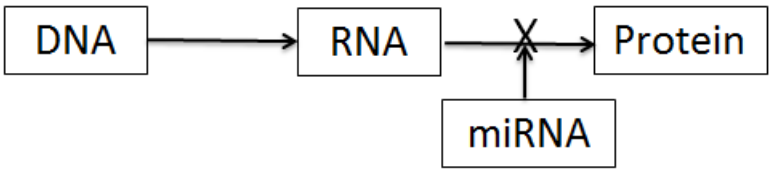


- DARS utilizes advanced 'humanized' mouse models that have either a human immune system, a human liver or both
- These models serve to better understand safety concerns for both small and large molecule drug products
- Are being used to assess biosimilar vs. originator biologics, toxicity, hypersensitivity, drug metabolism and drug-induced liver injury

Slide adapted from Kristina Howard, FDA/DARS
http://www.fda.gov/Drugs/ScienceResearch/ucm294603.htm#humanized

Novel MicroRNA Biomarkers: Application Pancreatic Injury

- Traditional serum biomarkers (amylase, lipase) of pancreatic injury have less than ideal sensitivity and specificity
- MicroRNAs (miRNAs) are short noncoding RNA molecules that bind to target mRNA causing gene silencing



- Tissue injury can rapidly release tissue-specific miRNAs that are very stable in biofluids = Biomarkers!
- Series of DARS studies in mice, rats and dogs
  - Equivalent or better sensitivity, more specific, larger range of response

Slide adapted from Rodney Rouse & Karol Thompson, FDA/DARS
http://www.fda.gov/Drugs/ScienceResearch/ucm294603.htm#druginduced

Chemical Informatics Research

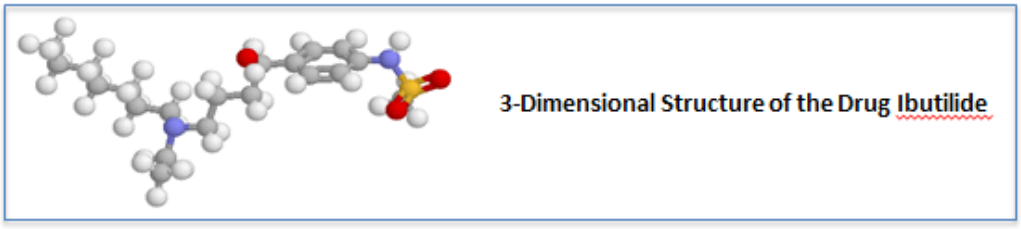
- **DARS Chemical Informatics Program performs research to**
  - Create chemical structure-linked toxicological and clinical effect databases
  - Develop rules for quantifying in vitro, animal and human endpoint data
  - Develop prediction models through collaborations

Ongoing Research Projects

- Develop (quantitative) structure activity relationship ((Q)SAR) models for bacterial mutation compliant with ICH M7
- Enhance (Q)SAR models for carcinogenicity and ICH S2 genetic toxicity endpoints

Emerging areas

- Evaluate (Q)SAR modeling for speeding development of drugs for severely debilitating and life threatening diseases



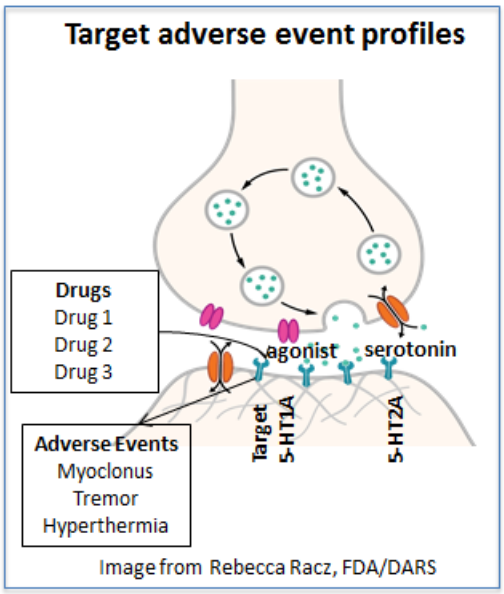
Slide adapted from Naomi Kruhlak, FDA/DARS
http://www.fda.gov/Drugs/ScienceResearch/ucm294603.htm#Computational

Bioinformatics Research

- Clinical trials do not identify many serious adverse events that ultimately lead to safety label changes

- DARS performs research to advance and validate methods in biomedical informatics to enhance pharmaco- vigilance and inform drug labeling

- DARS is evaluating the performance of software that generates target adverse event profiles; the set of adverse events associated with a pharmacological target



Slide adapted from Keith Burkhart, FDA/DARS

Regulatory Review Consults

Chemical Informatics Consults

- In FY16, performed 225 (Q)SAR consults for 492 drugs, drug impurities, metabolites and packaging leachables
  - Bacterial mutagenicity models in high demand due to ICH M7
  - Additional **nonclinical** (carcinogenicity, mutation, genetic toxicity, reproductive/developmental toxicity, phospholipidosis) and **clinical** (liver, cardiovascular, kidney/bladder effects) **models**
  - Consult distribution: 20% new drug products, 80% generics

Biomedical Informatics and General Division Consults

- Consults start with review of existing data and literature, incorporate biomedical and chemical informatics analyses and sometimes extend to laboratory investigations

Moving Forward …

- We want to modernize pharmacology and toxicology to advance drug development!
- We want to move new science into the regulatory review process!
- Opportunities for advancing CDER-NCTR collaborations
  - Collaborate on research with experimental or computational work occurring at NCTR and CDER, tackling complementary aspects of a project
  - Further engage CDER scientists
  - Validate and translate laboratory and computational models into the CDER review process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