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
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Office of New Drugs, CDER, FDA
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

- **CDER**
  Center for Drug Evaluation & Research

- **OND**
  Office of New Drugs

- **DNDP**
  Div. NonPrescription Drug Products
  - Oxybenzone
  - Reprotox
  - Triclosan
  - Carci

- **DAAP**
  Div. Anesthesia, Analgesia, Addiction
  - Pediatric Anesthetics
  - CNS Safety

- ~15 Review Divisions, multi-disciplinary by Therapeutic Area
- ~5 to 30 P/T per Division, ~185 reviewers
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
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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


Example of Optical Imaging with Voltage Sensitive Dyes

- Action potential duration
- Arrhythmias

Seconds

0.0 0.5 1.0 1.5

Seconds

0 5 10 15
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
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