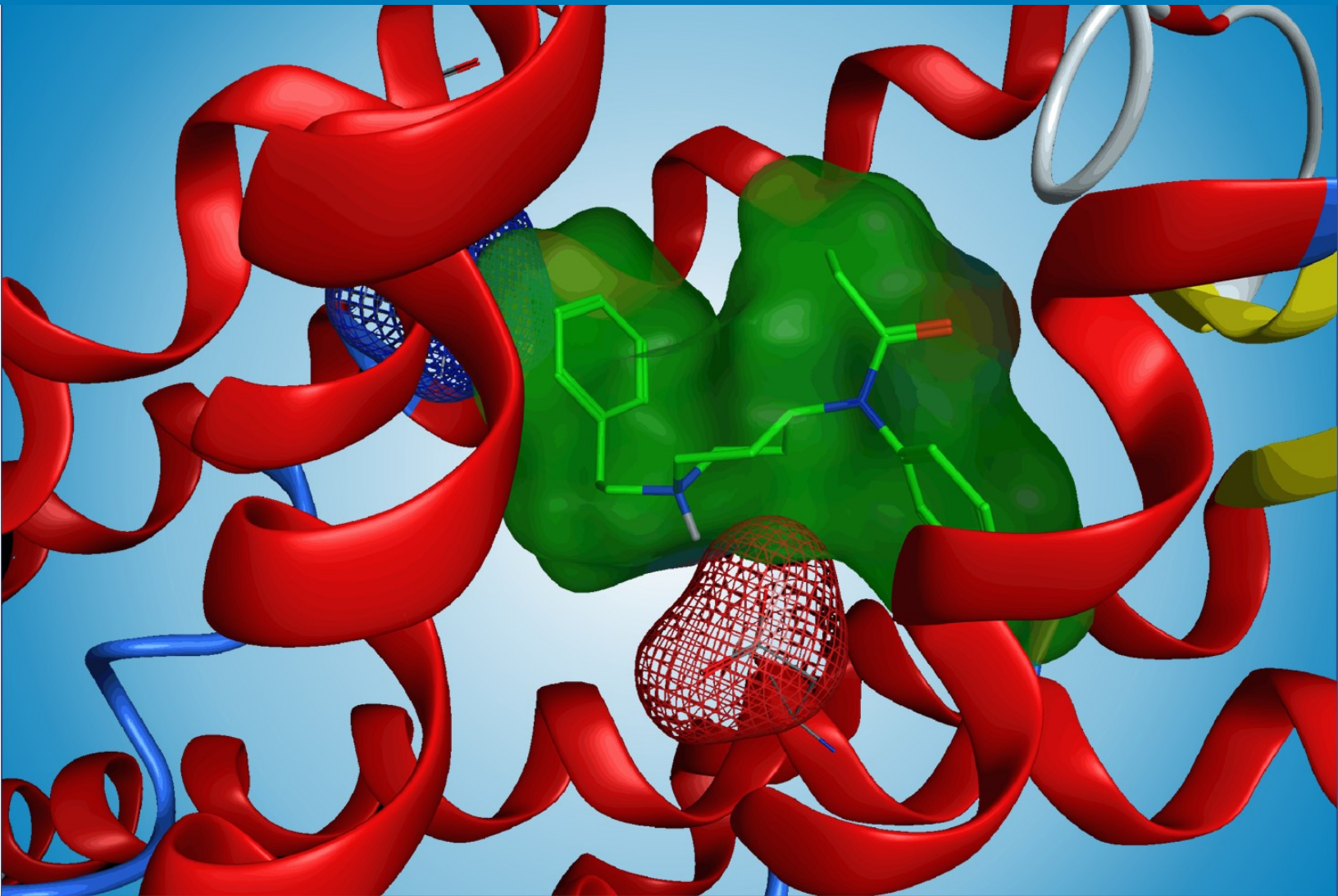


Division of Applied Regulatory Science

Annual Report

2019



Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research
Food and Drug Administration

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DIRECTOR'S MESSAGE

Our Division is unique in that we perform mission-critical applied research and review across the translational research spectrum including in vitro and in vivo laboratory research, in silico computational modeling and informatics, and integrated clinical research covering clinical pharmacology, experimental medicine, and postmarket analyses. Furthermore, our work spans all areas of drug development and evaluation, including new drugs, generic drugs, biosimilar drugs and over-the-counter drugs.



In 2019, we made exciting advances across all of these areas. Our clinical study on the systemic absorption of sunscreen ingredients was the most read *JAMA* article published in 2019. We continue to develop and validate in vitro and in silico models to improve assessment of drug safety, including liver and heart microphysiological systems and improved quantitative structure activity relationship (QSAR) models to assess mutagenicity of drug impurities. A series of publications demonstrated the utility of a humanized mouse model to study immune-mediated adverse effects of biological drugs. And we advanced multiple projects across all parts of the translational research spectrum studying opioids and other drugs of abuse. This and much more is described in our annual report.

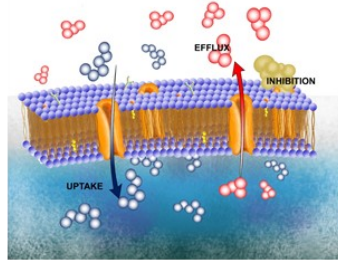
I am honored to be a part of this multi-disciplinary, collaborative team that moves new science into the drug evaluation process. We look forward to 2020!

David Strauss, MD, PhD
Director, Division of Applied Regulatory Science

RESEARCH OVERVIEW

The Division of Applied Regulatory Science (DARS) within FDA’s Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research (CDER) is a multidisciplinary research division that integrates scientific innovation and regulatory review. DARS forms teams “on-demand” to perform mission-critical research and expert regulatory review consultations.

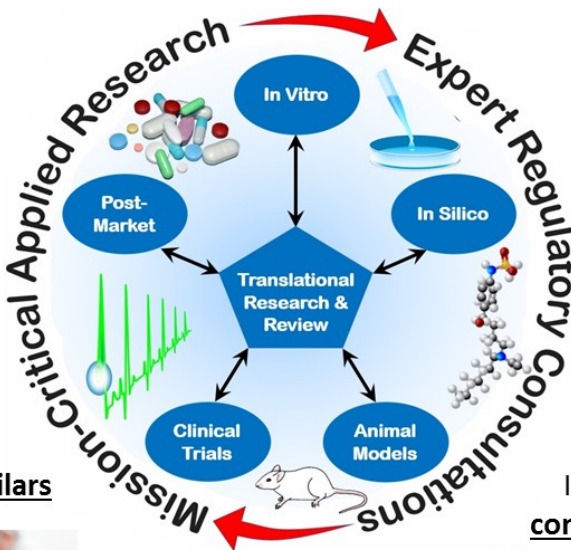
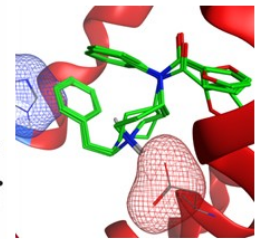
In vitro drug interaction studies for over-the-counter drugs



Integrated mechanistic assessment for postmarket safety signals



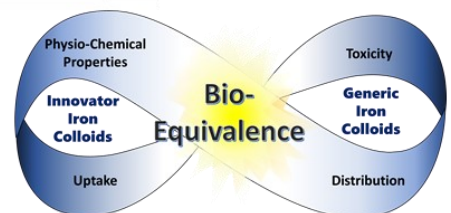
Computational modeling for drugs with abuse potential



Clinical studies for biomarkers for new drugs and biosimilars



In vivo models for complex generic drugs



RESEARCH OVERVIEW

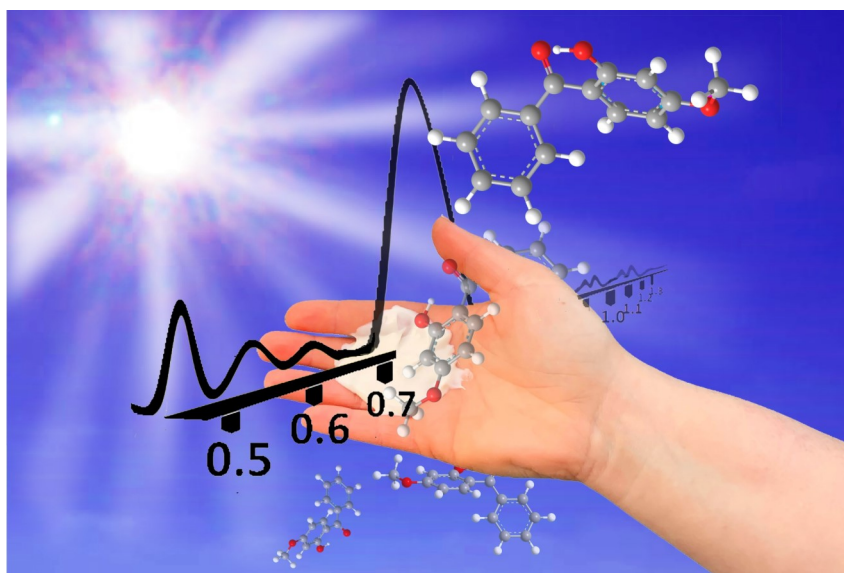
Over-the-Counter Research

Evaluation of Sunscreen Active Ingredients

Sunscreen Clinical Trial to Quantify the Systemic Absorption of Sunscreen

Ingredients: FDA has provided guidance that sunscreen active ingredients with systemic absorption greater than 0.5 ng/mL or with safety concerns should undergo expanded nonclinical toxicology assessment. DARS conducted a randomized clinical trial which demonstrated systemic exposure of 4 commonly used sunscreen active ingredients on application of sunscreen products under maximal use conditions consistent with current sunscreen labeling (ie, apply at least every 2 hours). All 4 sunscreen active ingredients tested resulted in exposures exceeding 0.5 ng/mL. The clinical effect of plasma concentrations exceeding 0.5 ng/mL is unknown, necessitating further research.

Matta et al. [JAMA 2019, 321\(21\):2082-91.](#)



Evaluation of in vitro Metabolism and Transporter-based Drug Interactions with

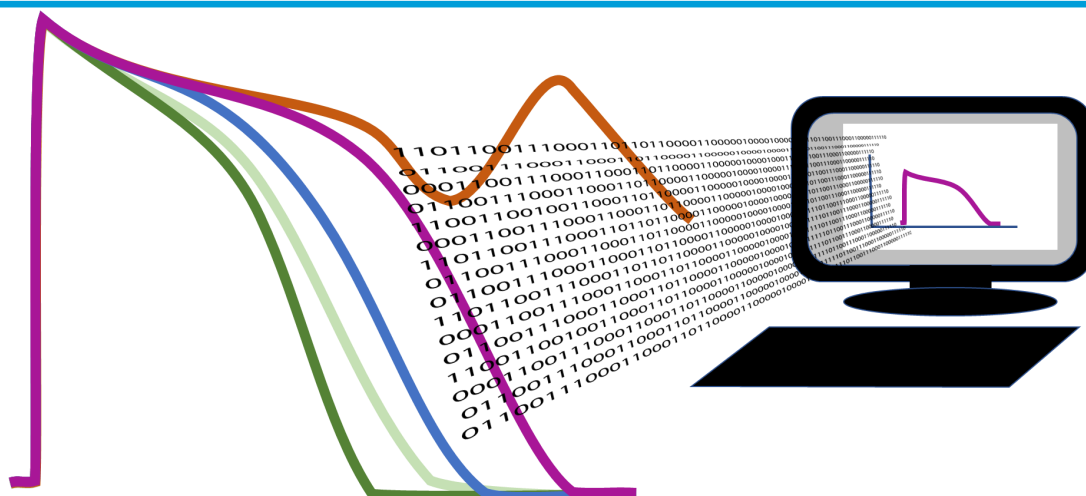
Sunscreen Active Ingredients: Percutaneously absorbed sunscreen active ingredients may have the potential to interact with other concomitantly administered drugs in humans. Sunscreen active ingredients are being examined for inhibition effects on metabolism catalyzed by cytochrome P450 (CYP) enzymes and for uptake by drug transporters.

RESEARCH OVERVIEW

Pre-Market Research: Safety

The Comprehensive in vitro Proarrhythmia Assay (CiPA)

The Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative involves testing a drug's potential to cause arrhythmias by using combined in vitro and in silico models. The goal is to inform on the actual arrhythmia risk of a drug, reducing the need for dedicated cardiac safety studies and better informing drug labeling.



Ion Channel & In Silico: The core of CiPA focuses on measuring the effects of a drug on multiple cardiac ion channels and integrating the information together in a computer model of the human heart cell. DARS is systematically assessing the data quality criteria and establishing best practices to be able to use this data for regulatory purposes. In addition, DARS performed a robust assessment of the computer model's ability to predict the risk of arrhythmia.

Li et al. [CPT Pharmacometrics Syst Pharmacol 2019, 8\(6\):371-9.](#)

Li et al. [Clin Pharmacol Ther 2019, Epub.](#)

Wu et al. [J Pharmacol Toxicol Methods 2019, 100:106605.](#)

Myocytes & Clinical ECG: The latter two components of CiPA focus on checking for missed or unanticipated effects. To assess the ability of human-induced pluripotent stem cell-derived cardiomyocytes, DARS sponsored an international multisite study. To assess the ability of electrocardiographic (ECG) biomarkers, DARS ran a phase 1-type ECG biomarker clinical study.

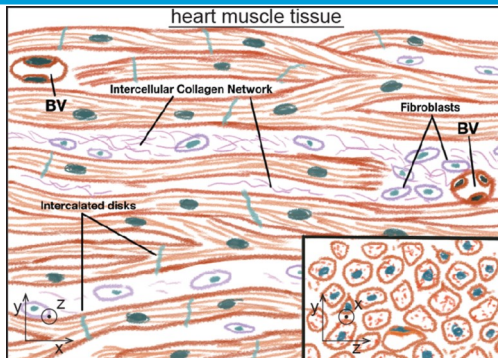
Matta et al. [J Anal Toxicol 2019, Epub.](#)

Blinova et al. [Clin Trans Sci 2019, 12\(6\):687-97.](#)

RESEARCH OVERVIEW

Pre-Market Research: Safety

Microengineered Stem Cell–Derived Cardiac Myocytes with Enhanced Maturity

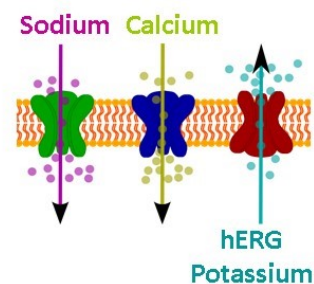


The usefulness of cardiac myocytes derived from pluripotent stem cells for predicting clinical drug effects is limited by characteristics of these cells that fail to replicate physiological settings that define primary mature human tissue. CDER scientists are microengineering stem cell–derived myocytes at the single-cell and tissue levels so they will become similar to mature cardiomyocytes.

Ribeiro et al. [Front Pharmacol 2019, 10:934.](#)

Experimental Factors That Impact Cardiac Late Sodium Channel and L-Type Calcium Channel Pharmacology

Drug potency on ion channels assessed using patch clamp methods are known to be voltage protocol-dependent. However, it is unclear whether additional experimental factors, including salt solutions used, and data analysis plan, affect drug potency estimation. This study focuses on identifying experimental factors that affect late sodium and L-type calcium current pharmacology.



Cardiac Safety Testing for Oligonucleotides and Peptides

International Council on Harmonisation (ICH) S7B and E14 guidelines outline cardiac safety testing strategies for small molecule drugs. However, oligonucleotides and peptides are larger in size, and there is currently no consensus regarding the panel of nonclinical cardiac safety tests for these drugs. This project uses nonclinical and clinical studies to evaluate if oligonucleotide and peptide drug applications should be evaluated under ICHS7B and E14 guidelines.

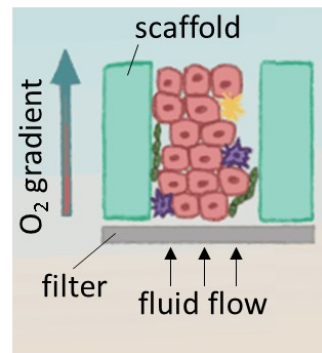
RESEARCH OVERVIEW

Pre-Market Research: Safety

Liver Microphysiological Systems for Predicting Clinical Drug Effects

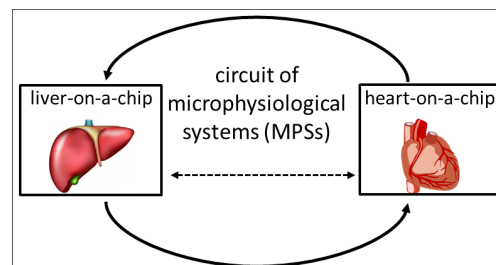
Liver microphysiological systems allow for the testing of chronic drug effects, drug–drug interactions, and drug-activated mechanisms involving multiple differentiated cell types. CDER researchers have conducted initial evaluations of liver microphysiological systems to support the systems’ utility for the study of drugs with hepatotoxic effects.

Ribeiro et al. [Clin Pharmacol Ther 2019, 106\(1\):139-47.](#)



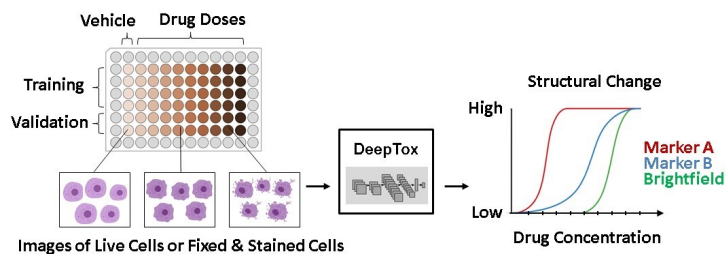
Interconnected Heart-Liver On-a-Chip Systems

A given drug may have toxic effects in multiple organs and drug toxicity may depend on liver metabolism. CDER scientists are studying how liver microphysiological systems interconnected with heart-on-a-chip systems can be used to predict drug effects that depend on liver metabolism or cause dual-organ toxicity.



Artificial Intelligence to Predict Drug Toxicity from Images of iPSC-Differentiated Cells

To evaluate cellular drug-induced structural toxicity, intracellular structures are labeled and imaged using high-content microscopy to detect intracellular damage with image analysis techniques. This project evaluates a novel image-based artificial intelligence tool for quantifying subtle structural changes in cell-based models.

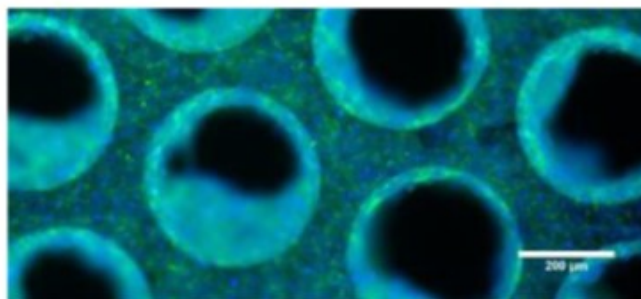


RESEARCH OVERVIEW

Pre-Market Research: Safety

Evaluation of Human Induced Pluripotent Stem Cell-Derived Hepatocytes as Models of Hepatic Function and Toxicity

This investigation compares induced pluripotent stem cell (iPSC)-derived hepatocytes in planar and spheroid form to primary human hepatocytes in assays of hepatocyte function (drug metabolism and transport) and drug toxicity, to assess their utility in drug development. The study focuses on phase II metabolism in these systems, specifically sulfation and glucuronidation.

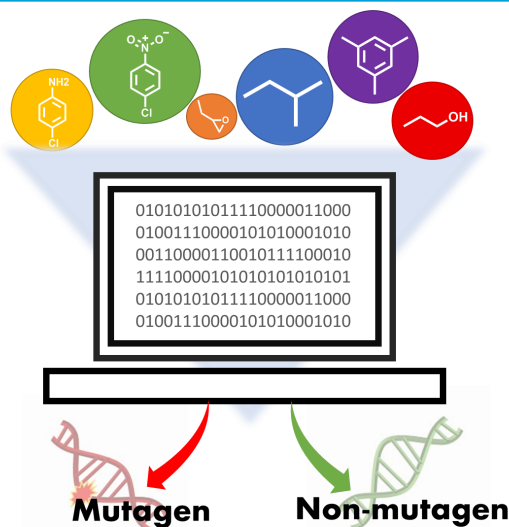


Indapurkar et al. [J Chromatogr B Analyt Technol Biomed Life Sci 2019, 1126-27:121765.](#)

Development of ICH M7 Compliant QSAR Models for Predicting Bacterial Mutagenicity

DARS has developed two new statistical bacterial mutagenicity (Q)SAR models that satisfy the International Council on Harmonisation (ICH) M7(R1) guideline that describes the use of complementary (quantitative) structure-activity relationship ((Q)SAR) models to assess the mutagenic potential of drug impurities in new and generic drugs. The newly-constructed bacterial mutagenicity models maintain good sensitivity and negative predictivity while showing greater coverage of proprietary pharmaceutical chemical space.

Landry et al. [Regul Toxicol Pharmacol 2019, 109:104488.](#)



RESEARCH OVERVIEW

Pre-Market Research: Safety and Availability

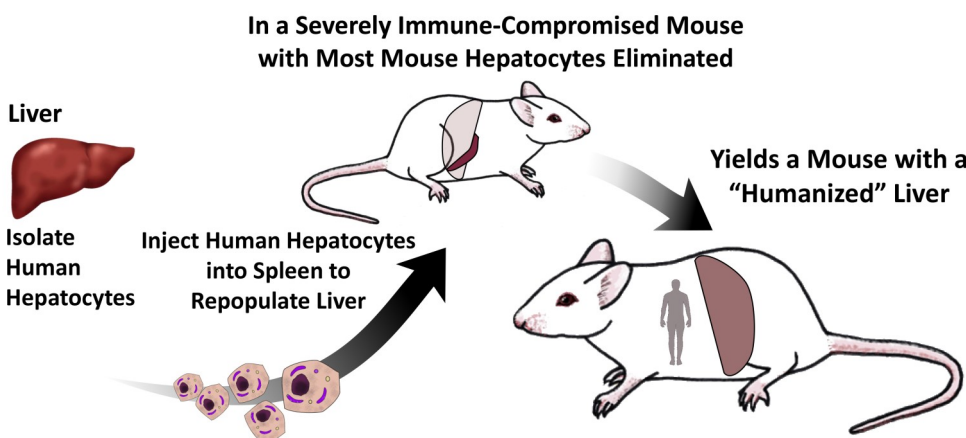
Developing a Novel Text-Mining Algorithm to Update the FDA Relevant Pediatric Molecular Target List

In August 2018, under the FDA Reauthorization Act (FDARA), FDA’s Oncology Center of Excellence Pediatric Oncology Program posted a public list of more than 190 molecular targets to provide better guidance to industry in planning for initial pediatric study plan submissions (the Pediatric Molecular Target List). As there is no standardized method for updating the list, DARS is developing a text-mining algorithm to identify relevant genes from literature for addition to the list.



Humanized Mouse Model as a Preclinical Tool to Study Human Drug Metabolism and Hepatotoxicity

Making a Mouse with a Human Liver



Screening drugs using animal models that closely mimic human drug metabolism can provide early insights into the risk of therapeutic drugs causing hepatotoxicity in humans. Liquid chromatography-

tandem mass spectrometry (LC-MS/MS)-based quantification of drugs and their metabolites in serum is used to identify human-specific metabolism.

RESEARCH OVERVIEW

Biosimilar and Generic Drug Research: Efficacy

Pharmacodynamic Biomarkers for Biosimilar Approval

To ensure US patients realize the public health benefit of a robust, competitive market for biosimilar products, FDA is focused on improving the efficiency of biosimilar development. DARS is conducting research to inform FDA's thinking on critical aspects of the use of pharmacodynamic biomarkers to demonstrate biosimilarity, which can either streamline or negate the need for comparative clinical studies. This project will result in an evidentiary framework and methodology for identifying, characterizing and applying biomarkers to serve as primary clinical assessment for biosimilar approval. Three clinical studies are being performed to characterize biomarkers for biosimilar development.

Li et al. [Clin Pharmacol Ther 2020; 107:40-42.](#)



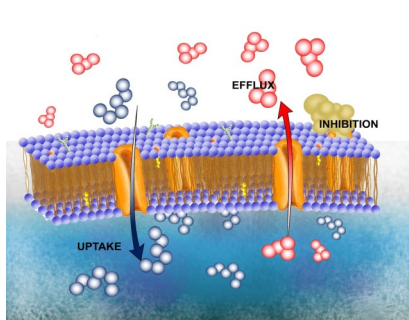
Evaluating the Utility of Transcriptomic Data: This project aims to explore the use of genome-wide transcriptional expression data from cultured human cells treated with reference and biosimilar drugs and simple pattern-matching algorithms that may enable the discovery of a biosimilar profile through the transitory feature of common gene-expression changes.

Profiling Circulating RNA as Potential Biomarkers: DARS has successfully optimized a Next Generation Sequencing (NGS) method for exploring the utility of small RNAs (including miRNA) as potential pharmacodynamic biomarkers of biosimilarity. The team is using both in vitro and in vivo approaches to assess and validate the utility of this approach as well as the analytical framework.

RESEARCH OVERVIEW

Biosimilar and Generic Drug Research: Safety

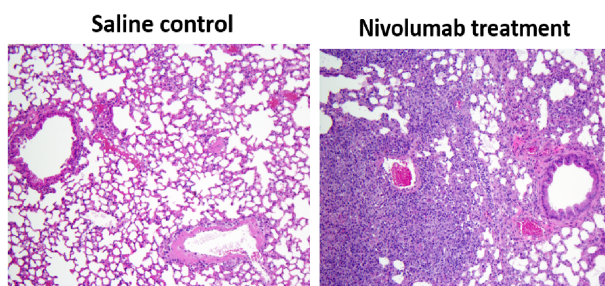
Interplay Between OAT2 and CYP2C9 in Warfarin and Tolbutamide Drug-Drug Interactions



Clearance mechanisms, such as the hepatic OAT2 transporter, for warfarin and tolbutamide are utilized as index substrates of CYP2C9 for clinical drug-drug interaction (DDI) studies. This project will identify drugs that interact with warfarin or tolbutamide and determine the mechanism(s) for interaction. These cases will identify if additional insights into OAT2 are needed.

Immune-Mediated Adverse Effects of Biological Drug Products

Cancer Checkpoint Inhibitor-Induced Pneumonitis in Humanized Mice



While significant progress has been made in engineering biological products, the human immune system may still produce an immune response to the product resulting in poor efficacy or life-threatening reactions. DARS is evaluating a humanized mouse model to predict immune-mediated adverse effects of biological products.

Semple et al. [Clin Transl Sci 2019, 12\(3\):283-90.](#)

Yan et al. [Transl Res 2019, 210:43-56.](#)

Weaver et al. [Toxicol Sci 2019, 169\(1\):194-208.](#)

Yan et al. [Toxicol Appl Pharmacol 2019, 372:57-69.](#)

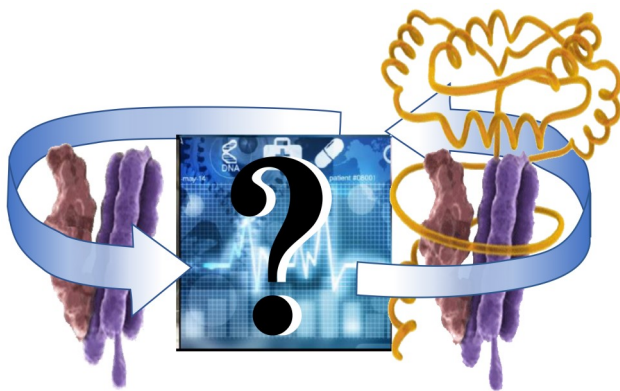
Evaluating Immunogenicity for Impurities Found in Peptide Generic Drugs

This project is evaluating the immunogenicity of generic peptide products, such as teriparatide and liraglutide, with a focus on the peptide related impurities and host cell related impurities. DARS is utilizing in vitro and in vivo techniques to assess their immunogenic potential.

RESEARCH OVERVIEW

Biosimilar and Generic Drug Research: Quality and Availability

Impact of PEG Variability on Biological Drug Quality, Pharmacokinetics and Biosimilarity Assessment



Filgrastim

~

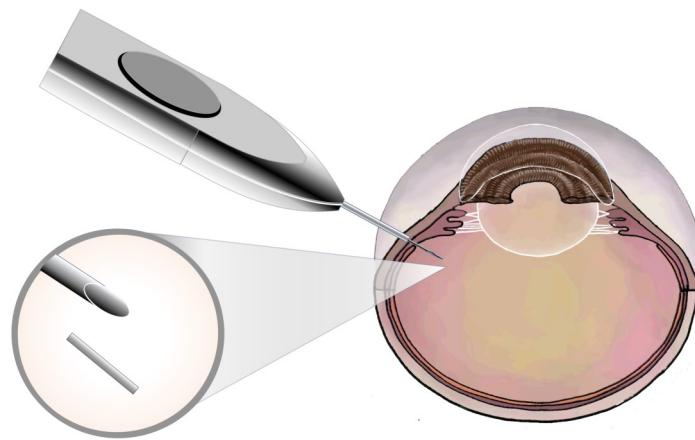
Pegfilgrastim

To address the challenges associated with determining pharmacokinetic/ pharmacodynamic biosimilarity of PEGylated products, DARS has initially focused on evaluation of assays used for PEGfilgrastim products. By assessing the suitability of different bioassays across different drug matrices, we can better estimate their ability to support pharmacokinetic assessment new biosimilar drug applications. These

studies will then extend to other PEGylated products for which similar issues may be encountered.

Determining Intravitreal Implant Product Bioequivalence

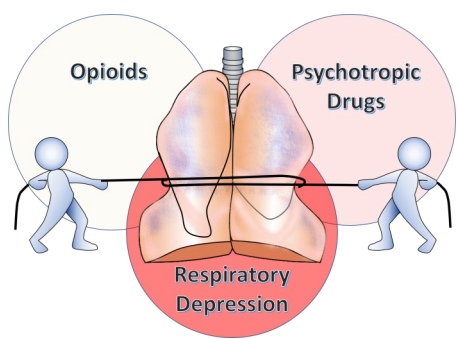
This project is a preliminary investigation to estimate the systemic dexamethasone level after a single intravitreal implantation of 0.7 mg dexamethasone implant in a rabbit eye model. The data on systemic dexamethasone exposure may offer a relatively non-invasive surrogate biomarker of intra-ocular exposure for assessing bioequivalence of generic implant products.



RESEARCH OVERVIEW

Drugs with Abuse Potential Research

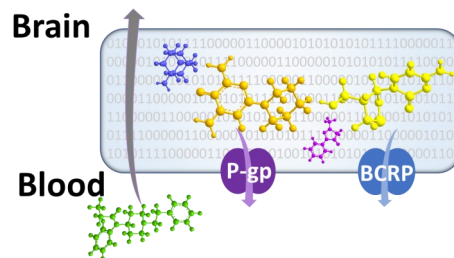
Clinical Study to Investigate the Effect of Psychotropic Drugs on Opioid-Induced Respiratory Depression



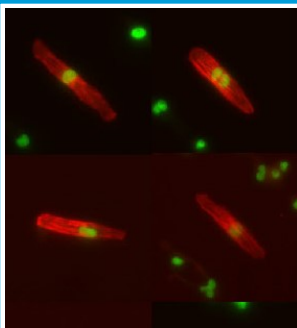
FDA recently added black box warning to drug labels for opioids and benzodiazepines to not co-administer due to risk for respiratory depression; it is unclear whether other psychotropic drugs can have a similar effect when co-administered with opioids. The primary objective of this project is to study whether two psychotropic drugs increase opioid-induced respiratory depression when co-administered.

Blood Brain Barrier In Silico Model

Drugs that cross the blood brain barrier (BBB) may have psychotropic effects. Therefore, DARS is developing computational models that use chemical structure to predict drug permeation at the BBB, as well as, interactions with major transporters (P-gp, BCRP). These models can be rapidly deployed and used to complement predictions from the Public Health Assessment via Structural Evaluation (PHASE) protocol and predict potential neurotoxic effects.



Effects of Buprenorphine, Norbuprenorphine, Methadone, Naltrexone, and Naloxone on Cardiac Ion Channels

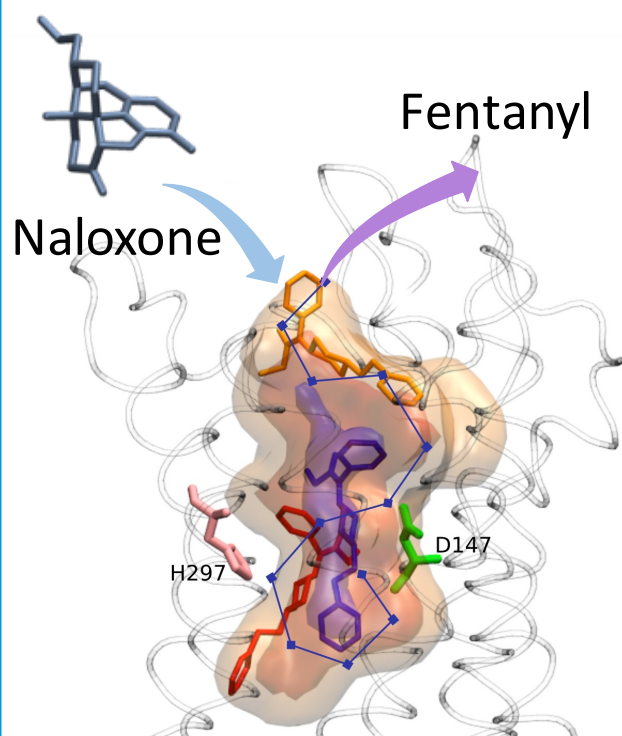


Buprenorphine causes concentration-dependent QTc prolongation. This study investigates whether acute block of cardiac ion channels by buprenorphine and its major metabolite norbuprenorphine contributes to drug's QTc prolongation. For comparison, methadone, naltrexone, and naloxone were also studied.

RESEARCH OVERVIEW

Drugs with Abuse Potential Research

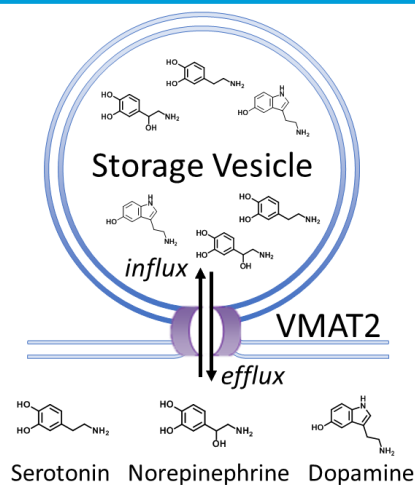
Calculating Kinetic Parameters of Opioids



These projects aim to develop and validate *in silico* models to calculate kinetic parameters of opioids at the mu opioid receptor and predict the amount of naloxone needed to overcome opioid-induced respiratory depression. These models will be incorporated into the Public Health Assessment via Structural Evaluation (PHASE) protocol and provide invaluable information to the FDA and DEA for assessing the risk of newly identified opioids to public safety.

Evaluating and Predicting Drug Effects at the Vesicular Monoamine Transporter 2

This research initiative provides the first systematic evaluation of drugs that interact with Vesicular Monoamine Transporter 2 (VMAT2). Experimental characterization of these drugs will allow for the construction of an *in silico* model that will use chemical structure to predict activity at VMAT2. The model will assist in the development of a screening protocol for new drugs that may require additional safety testing at VMAT2.

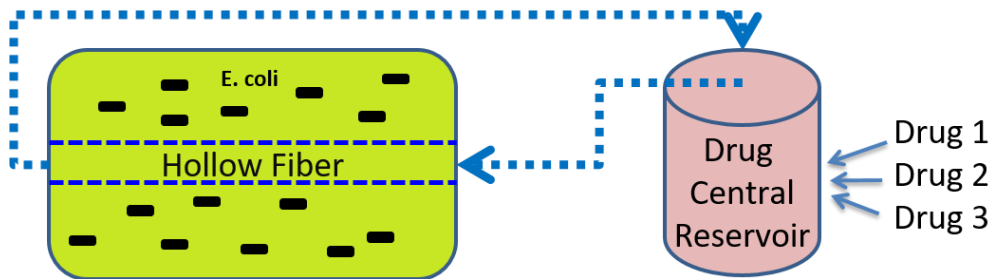


RESEARCH OVERVIEW

Post-Market Research: Safety and Efficacy

Assessing Antimicrobial Resistance

DARS has developed an *in vitro* method to quantitate the rate at which antibiotic resistance appears. The system uses a hollow fiber bioreactor system to deliver single drugs or combinations of drugs using human pharmacokinetic profiles. Additionally, next-generation sequencing is used to investigate the genetic and epigenetic biomarkers of antibiotic resistance, and genomics and bioinformatics are utilized to investigate the effects of oral antibiotics on *in vitro* bacterial genomes and *in vivo* gut microbiome.

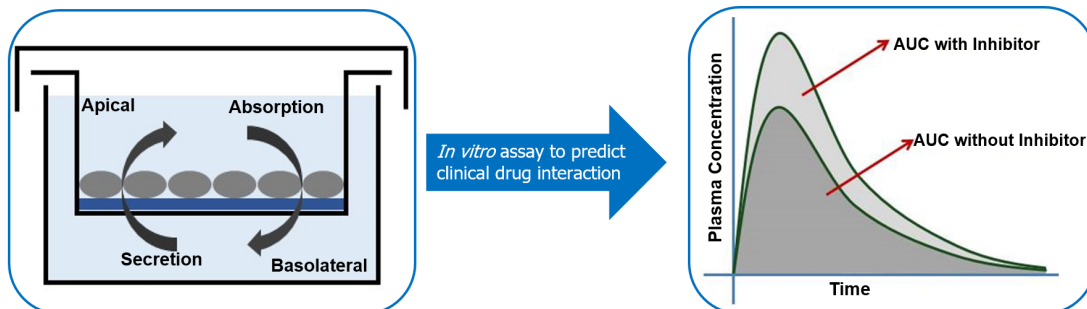


Chockalingam et al. [Antibiotics \(Basel\) 2019, 8\(4\):E170.](#)

Gandhi et al. [Future Sci OA 2019, 5\(1\):FSO349.](#)

Calculation of Efflux Ratios and IC50 Values for the Prediction of P-gp-Mediated Drug-Drug Interactions

The choice of cell line, e.g. Caco-2, LLC-PK1 or MDCK, may impact efflux ratios (for determining if a drug is a P-gp substrate) and IC50 values (for determining if a drug is a P-gp inhibitor). If there are differences, it must be determined which cell line is the most accurate in retrospectively predicting whether a drug is a substrate and/or inhibitor of P-gp. These data will assist in determining whether clinical drug-drug interaction studies will be needed for a new drug.



RESEARCH OVERVIEW

Additional Research

Bioanalytical Methods for Measuring Tacrolimus

DARS developed and validated a high-throughput bioanalytical method to determine the concentration of tacrolimus in human clinical study samples.

Development and Validation of an LC-MS/MS Assay for Methylphenidate

DARS generated quantitative data on dried blood spots as a benchmark for bioequivalence studies.

Evaluating Computational Models of Risk

DARS evaluated the accuracy of commercial target prediction platforms.

Exposure and Patient Characteristics for Torsade de Pointes

DARS is developing a text-mining algorithm to adjudicate Torsade de Pointes FAERS reports.

Public Health Assessment via Structural Evaluation (PHASE)

DARS uses multiple computational methodologies to evaluate the public health risk of a compound.

Oral Anticoagulation in Underrepresented Groups

DARS is studying sex- and race-specific outcomes associated with novel oral anticoagulants.

Overdose Labeling

DARS is evaluating the accuracy of the recommendations in the Overdose section of FDA labels.

Predicting Adverse Events from Molecular Targets

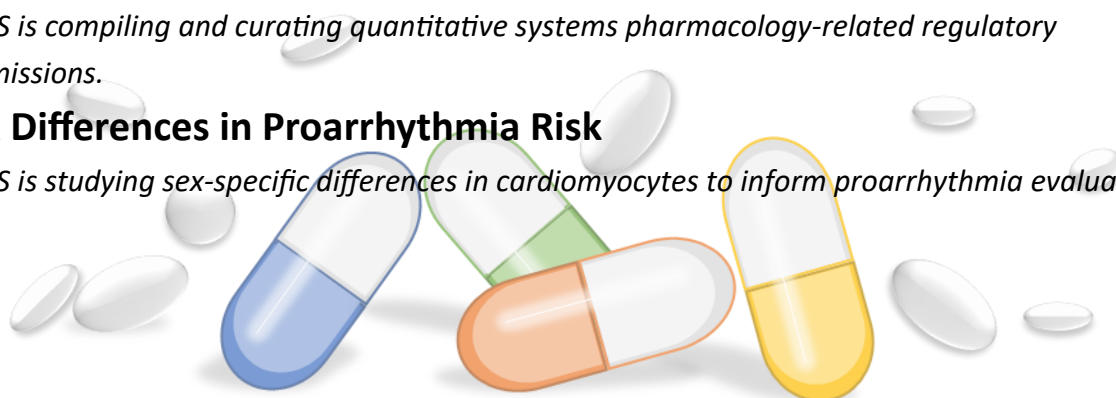
DARS uses computational models with post-market data sources to predict adverse events using shared targets.

Quantitative Systems Pharmacology Parameters

DARS is compiling and curating quantitative systems pharmacology-related regulatory submissions.

Sex Differences in Proarrhythmia Risk

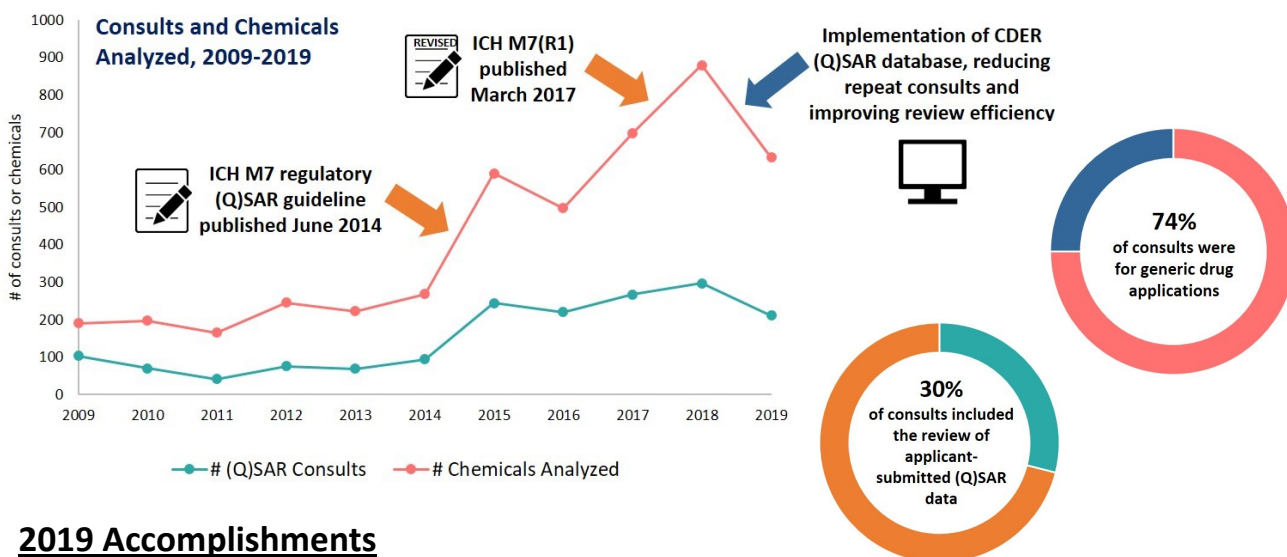
DARS is studying sex-specific differences in cardiomyocytes to inform proarrhythmia evaluation.



(Q)SAR CONSULTS

Computational Toxicology Consultation Service

FDA requires a rapid and effective way to predict the potential toxicity of components of drug products when faced with data gaps. The DARS Computational Toxicology Consultation Service provides (Quantitative) Structure Activity Relationship [(Q)SAR] analyses and structure-based search capabilities on a consultative basis using a range of in silico tools to predict toxicological outcomes such as genotoxicity, carcinogenicity, and drug-induced liver injury. In addition, consultations are provided to assist CDER safety reviewers in the interpretation of (Q)SAR data submitted to FDA by pharmaceutical companies. The Computational Toxicology Consultation Service provides, on average, consultations for 11 chemical structures per week.



2019 Accomplishments

- ◆ January: Rolled-out Panorama-based consultation process to support generic drug application and drug master file review
- ◆ July: Launched (Q)SAR database application on CDER server providing archived consultation reports and related toxicology data directly to reviewers with a structure-based search capability

Modernized structure registration and data curation process using an interactive and automated software application

- ◆ Co-authored three publications on new models and best practices:

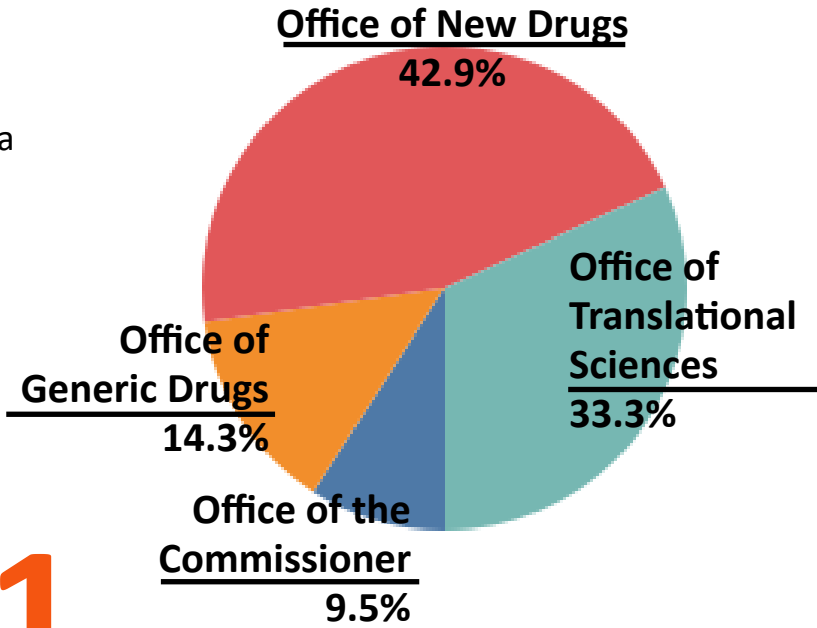
Amberg, et al. [Mutagenesis 2019, 34\(1\):67-82.](#)

Hasselgren, et al. [Regul Toxicol Pharmacol 2019, 107:104403.](#)

Landry et al. [Regul Toxicol Pharmacol 2019, 109:104488.](#)

DIVISIONAL CONSULTS

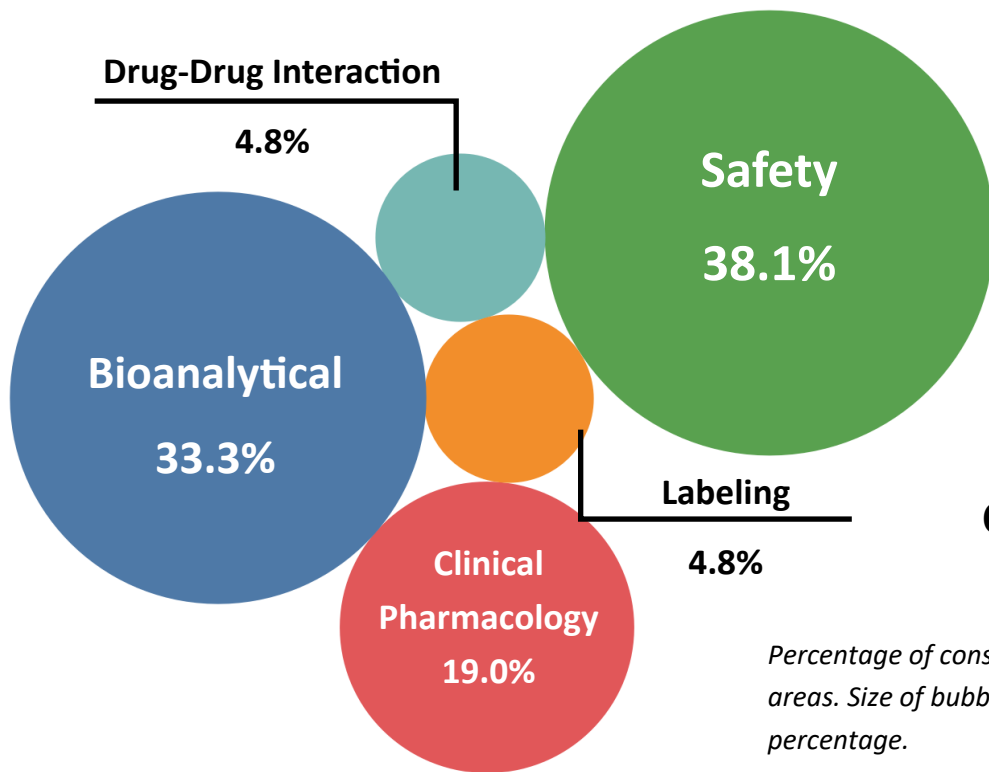
DARS provides expert regulatory review consultations that combine a critical review of existing knowledge, in silico computational analyses, in vivo and in vitro laboratory studies, and translational analysis of preclinical studies, clinical trials, and post-market data.



21

Consults completed

Percentage of consults completed for each FDA office.



5

Consult areas addressed

Percentage of consults in each of five topic areas. Size of bubbles corresponds to percentage.

ENGAGEMENT



Publications

Expert review provided for

6

intramural and extramural
funding programs



Presentations



Posters



DARS provided expert reviews for over 30 journals, including:

- | | | |
|---|--|---------------------------|
| Clinical Pharmacology and Therapeutics | Ecotoxicology and Environmental Safety | Pharmaceutical Research |
| Journal of American College of Cardiology | Toxicology Letters | Environment International |
| Bioinformatics | Journal of Cheminformatics | Pharmacotherapy |
| Nature Communications | Scientific Reports | PLOS ONE |

CONTACT US

Want to Learn More About DARS?

Regulatory Science Review Article

DIA

Translating New Science Into the Drug Review Process: The US FDA's Division of Applied Regulatory Science

Therapeutic Innovation
& Regulatory Science
1-12
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DOI: 10.1177/2168479017720249
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James Weaver, PhD¹, Keith Burkhart, MD¹, Vikram Patel, PhD¹,
and David G. Strauss, MD, PhD¹

Therapeutic Innovation & Regulatory Science 2018;52:244-255.

<https://doi.org/10.1177/2168479017720249>

**DARS Website: [www.fda.gov/about-fda/
center-drug-evaluation-and-research-cder/
division-applied-regulatory-science](http://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/division-applied-regulatory-science)**

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