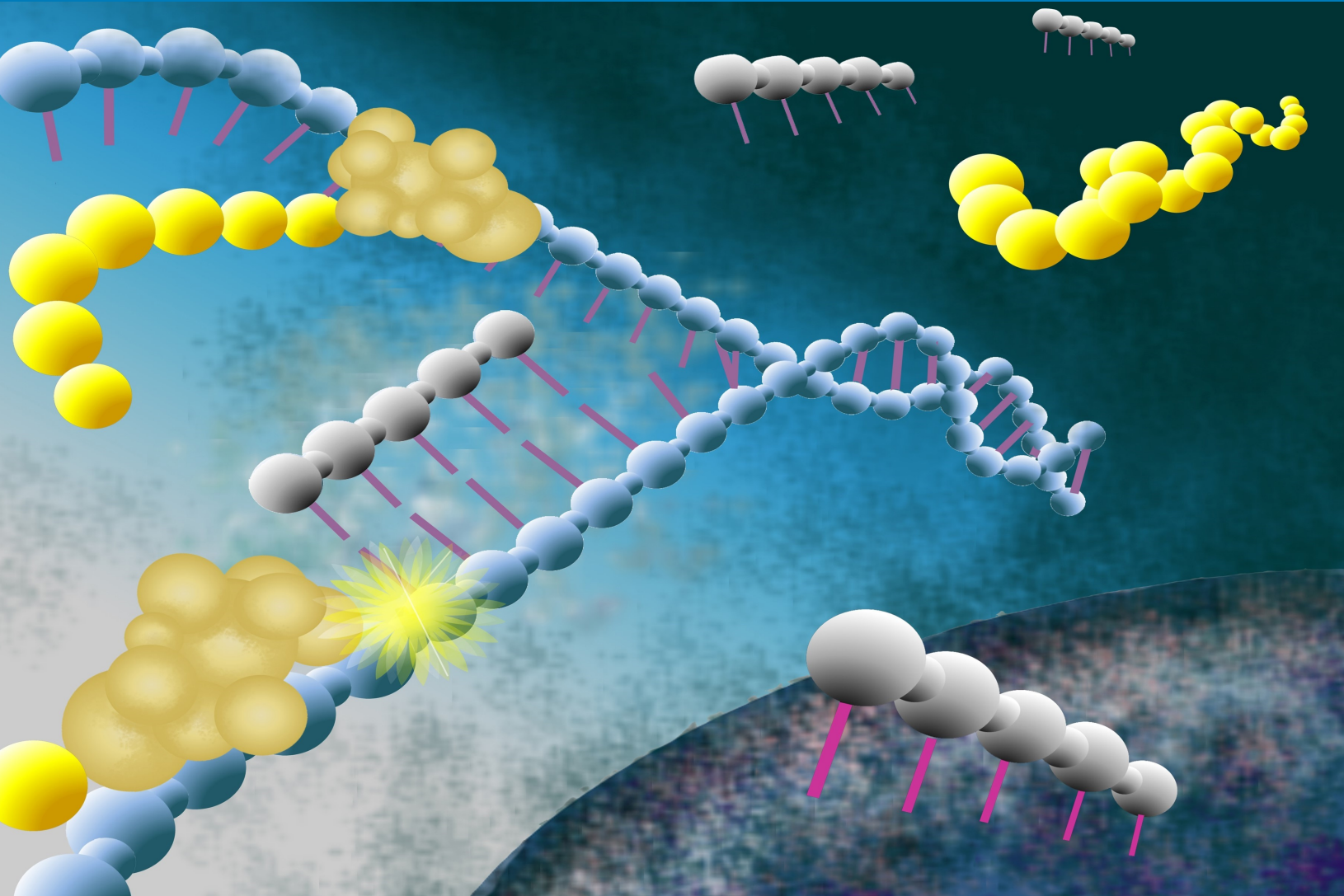


Division of Applied Regulatory Science

Annual Report

2018



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

Coming to work every day is exhilarating because we never know what question or problem is going to land on our desk. When scientific problems emerge throughout the Center for Drug Evaluation and Research (CDER) that our colleagues are unsure how to approach or have not seen before, they often consult us because of our ability to assemble diverse, multi-disciplinary teams to approach a problem from multiple angles and think outside the box. Our experts include pharmacologists, chemists, biologists, engineers, computational scientists, veterinarians, pharmacists, physicians and more. Our toolbox includes in silico computational models, in vitro assays, in vivo animal models, clinical trials and post-market analyses with real-world data. In 2018, we responded to multiple urgent needs to tackle different priority areas for CDER and FDA across all areas of drug development. Here are some highlights!

Drugs of abuse – The opioid epidemic has led to a rise in synthetic, designer street drugs that are being abused. We developed and applied a novel computational method to assess the risk of a synthetic drug to public safety before laboratory data can be obtained.

New drugs – We are assessing novel in vitro, in silico and in vivo models to further predict drug safety issues before the drugs are given to patients or reach the market. As one example, novel approaches we developed related to cardiac safety are being discussed by the International Council for Harmonisation of Technical Requirements for Human Use (ICH) to be implemented by regulatory agencies throughout the world.

Postmarket – Clinical trials performed before a drug's approval in many instances only include a limited number of patients. We are leveraging information from multiple clinical trials and data across drug classes to develop computational models to predict the risk of rare adverse events not seen in clinical trials and the safety and effectiveness of drugs in subgroups of patients.

Generic drugs and biosimilars – The availability of safe and effective generic drugs and biosimilars gives patients options and can bring down drug prices. Through in vitro, in vivo, in silico and clinical research, we are advancing the science of assessing complex generics and biosimilars to bring safe and effective options to patients faster.

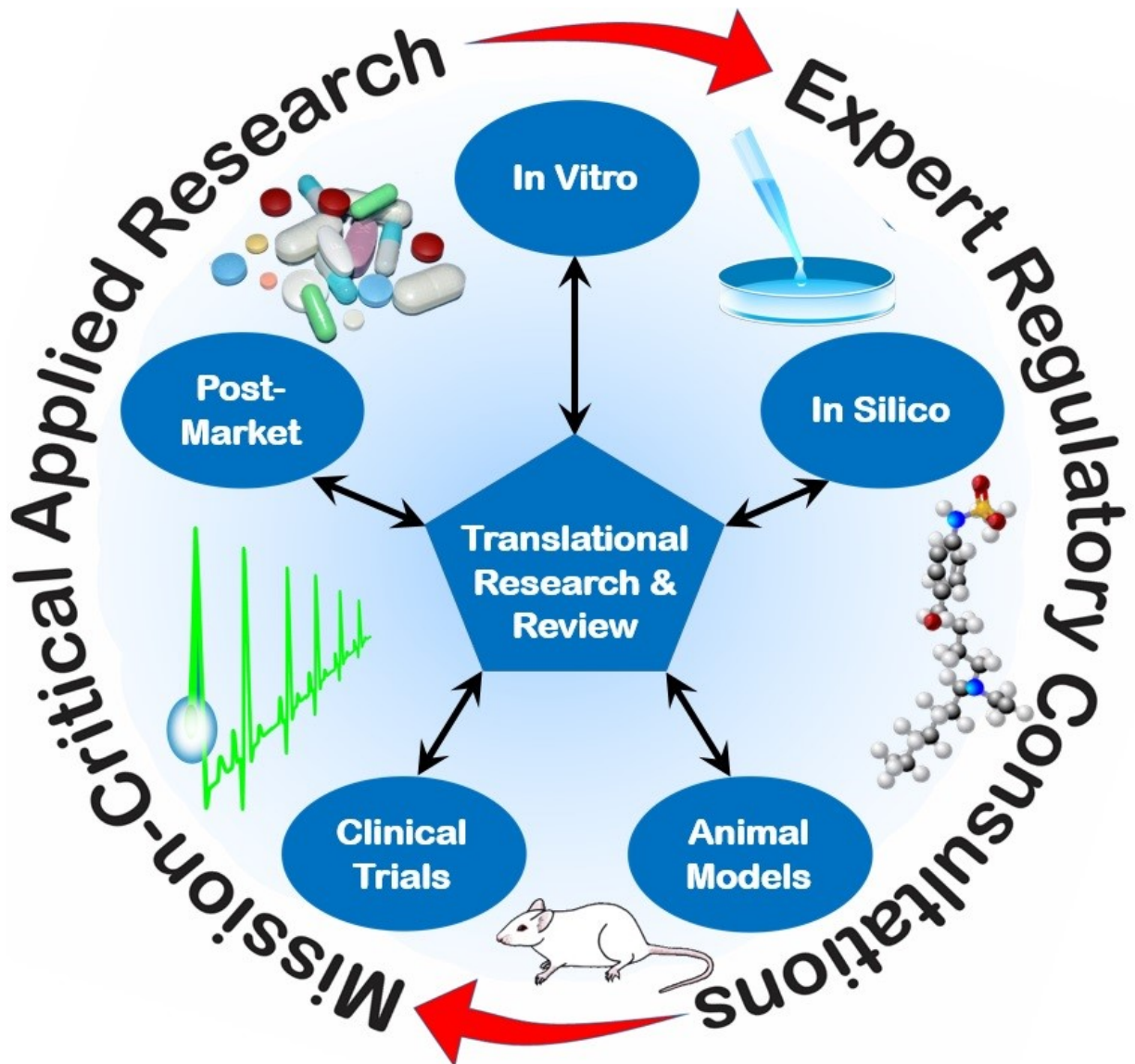
Over-the-counter (OTC) drugs – Sunscreens are a common OTC drug that were historically thought to not be absorbed systemically, however this no longer appears to be true. We are performing a clinical trial to assess the systemic absorption of common sunscreen products and assessing the drug-drug interaction potential of the sunscreen ingredients in vitro.

We are looking forward to continuing and expanding this work in 2019!

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.

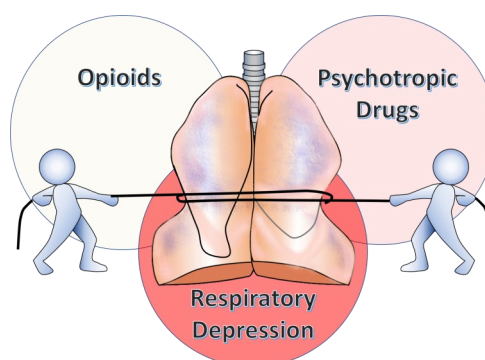


RESEARCH OVERVIEW

Drugs with Abuse Potential Research

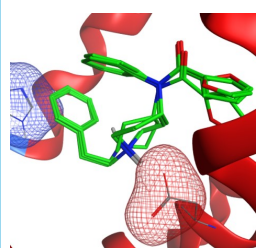
Effects of Co-administration of Opioid and Non-benzodiazepine Sedative Psychotropic Drugs on Respiratory Depression

Benzodiazepines have been found to potentiate respiratory depression when combined with an opioid and recently had their labels updated to reflect this. Together with CDER's Office of New Drugs and Division of Clinical Pharmacology I, DARS staff is investigating the risk for potentiated respiratory depression of an additional 13 psychotropic drugs alone and when co-administered with an opioid in a rat model.



Preclinical Research to Achieve Safer Prescribing of Psychoactive Therapeutics for Patients Who Use Opioids.
<https://www.fda.gov/Drugs/ScienceResearch/ucm615450.htm>

Computational Models to Predict Opioid Binding

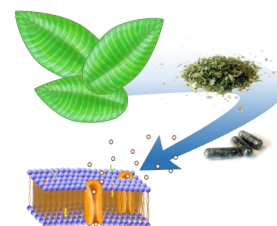


DARS developed and tested a molecular docking model to accurately predict the binding affinity of structurally diverse opioids at the mu-opioid receptor. This model provides a method for rapid evaluation of the risk of a newly identified drug to public safety.

Ellis, et al. Predicting opioid receptor binding affinity of pharmacologically unclassified designer substances using molecular docking. *PLoS ONE* 2018, 13(5):e0197734.

Evaluating Kratom Alkaloids (Components) using PHASE

Kratom is being sold and promoted as substitute for opioids for pain management and alleviating opioid withdrawal; however, kratom has no FDA-approved uses. DARS developed the Public Health Assessment via Structural Evaluation (PHASE), which incorporates multiple computational methodologies to provide a structure-based evaluation of a compounds' risk to public safety. DARS applied this methodology 25 kratom alkaloids (components).



Statement from FDA Commissioner Scott Gottlieb, M.D., on the Agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse.

<https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm595622.htm>

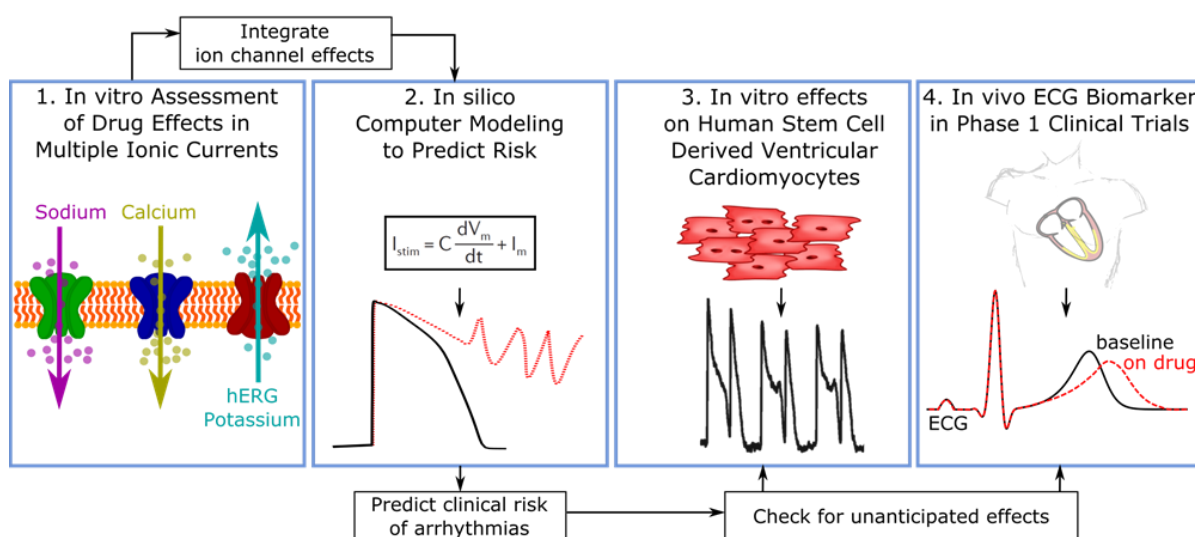
RESEARCH OVERVIEW

Pre-Market Research

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.

CiPA Phases 1-4



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. *Clin Pharmacol Ther.* 2018, doi: 10.1002/cpt.1184.

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.

Blinova, et al. *Cell Reports.* 2018;24(13):3582-92.

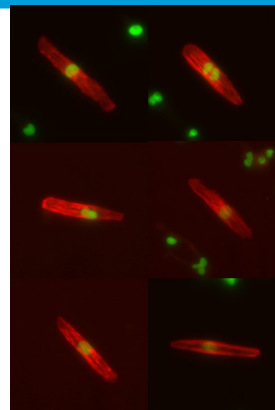
Vicente, et al. *Clin Pharmacol Ther.* 2018. doi: 10.1002/cpt.1303.

RESEARCH OVERVIEW

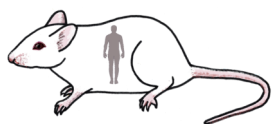
Pre-Market Research

Microengineered Induced Pluripotent Stem Cell–derived Cardiac Myocytes with Enhanced Maturity

The use of cardiomyocytes derived from induced pluripotent stem cells for predicting clinical drug effects is limited by the fact that these cells fail to replicate mature human tissue. DARS scientists are microengineering induced pluripotent stem cell-derived cardiac myocytes at the single-cell level to enhance their “maturity” so they can be used as better preclinical assays for drug development.



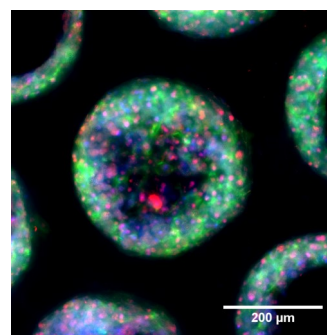
Humanized Mouse Model as a Preclinical Tool to Study Human Drug Metabolism and Hepatotoxicity



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.

Interconnected Heart-Liver On-a-Chip Systems

Drug toxicity may depend on liver metabolism, but these effects cannot be studied in isolation because organs interact within the body. DARS scientists are studying how interconnected liver and heart microphysiological systems can be used to predict drug effects that depend on liver metabolism or cause dual-organ toxicity.



RESEARCH OVERVIEW

Biosimilar and Generic Drug Research

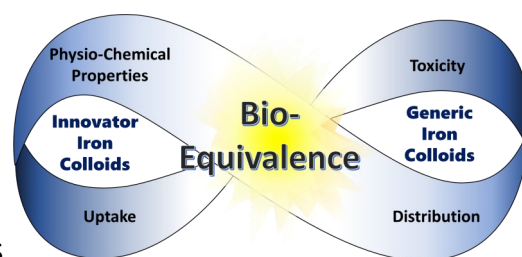
Pharmacodynamic Biomarkers to Support Biosimilar Approval

This project will advance the science of using biomarkers to assess biosimilarity and make biosimilar development more efficient in accord with the FDA Guidance for Industry on "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product." This supports the Biologics Price Competition and Innovation Act that created an abbreviated licensure pathway for biological products shown to be "biosimilar" to an FDA-licensed reference product.



Comparative Evaluation of Brand and Generic Sodium Ferric Gluconate Complex

In addition to the established approach of similar physicochemical and bioavailability, the European Medicines Agency (EMA) recommended cellular uptake and animal biodistribution studies to establish the bioequivalence of iron colloid generic drugs. Multiple in vivo and in vitro studies performed by DARS showed that generic and innovator products did not differ in physicochemical properties, toxicity, uptake, or distribution and that the additional cellular uptake and animal biodistribution studies did not add value. The results confirmed FDA's established approach.



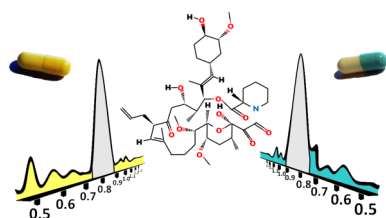
Sun, et al. [Nanomaterials 8\(1\), 25](#). Wu, et al. [Nanomaterials 7\(12\), 451](#).

Beekman, et al. [Nanomaterials 8\(1\), 10](#). Matta, et al. [Nanomaterials 2018, 8\(2\), 101](#).

RESEARCH OVERVIEW

Biosimilar and Generic Drug Research

Bioanalytical Method Development for Measuring Tacrolimus

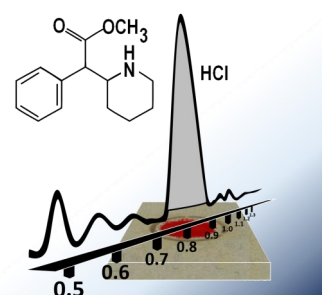


The bioavailability of dispersion drug products can differ from batch to batch

due to manufacturing inconsistencies and polymer carriers used in formulations. To evaluate these inconsistencies, a clinical study is being performed in healthy human subjects. DARS developed and validated a high-throughput bioanalytical method to determine the concentration of tacrolimus in human clinical study samples.

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

Analytical methodology metrics are currently lacking for use with dried blood spot analysis of generic drug bioequivalence. DARS generates quantitative data on dried blood spots, which provides a benchmark for bioequivalence studies in pediatrics.



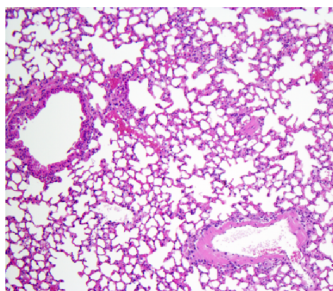
Gandhi, et al. *Bioanalysis* 2018, 10(11):839-50.

Immune-Mediated Adverse Effects of Biological Drug Products

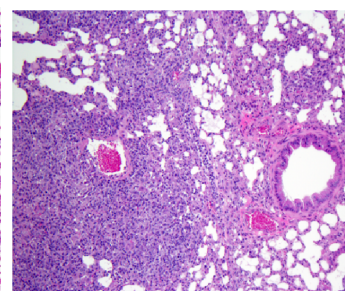
While significant progress has been made in engineering biological products, the human immune system may still produce an immune response to the product resulting in poor efficacy or life-threatening reactions. DARS is evaluating a humanized mouse model to predict immune-mediated adverse effects of biological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

Cancer Checkpoint Inhibitor-Induced Pneumonitis in Humanized Mice

Saline control



Nivolumab treatment

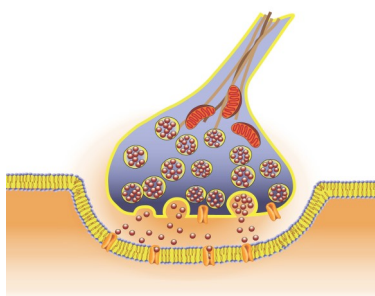


RESEARCH OVERVIEW

Post-Market Research

Predicting Adverse Events Based on Molecular Target

Drugs that share the same targets often cause the same adverse events. DARS uses multiple post-market sources to create computational models that predict adverse events for pre-market and newly marketed drugs. Validation studies are underway.



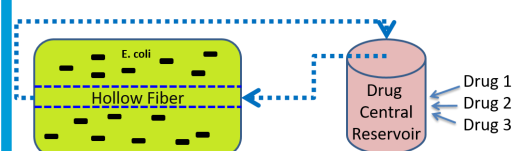
Schotland, et al. *CPT Pharmacometrics Syst Pharmacol* 2018, doi: [10.1002/psp4.12356](https://doi.org/10.1002/psp4.12356).

Racz, et al. *Clin Transl Sci.* 2018;11(3):322-9.

Subgroup Analysis of the Safety and Efficacy of NOACs

Non-vitamin K oral anticoagulants (NOACs) are a novel alternative to warfarin for preventing stroke in patients with atrial fibrillation. DARS is evaluating sex- and race-specific risks of stroke, bleeding and death associated with NOAC therapy by combining data from multiple clinical trials. New computational modeling methods and statistical approaches are being investigated to estimate the risks of outcomes in demographic subgroups.

Assessing Antimicrobial Resistance



Determining bacterial resistance to antibiotics by conventional methods (turbidometric, spectrophotometric or disk diffusion) is still a relatively slow process. To rapidly detect antibiotic resistance, liquid chromatography with tandem mass spectrometry-based methods are being used in in vitro hollow-fiber and in vivo mouse studies.

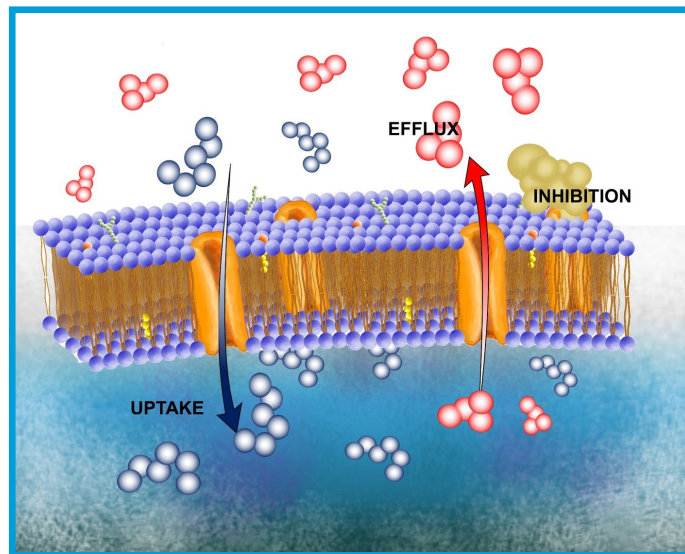


RESEARCH OVERVIEW

Over-the-Counter Research

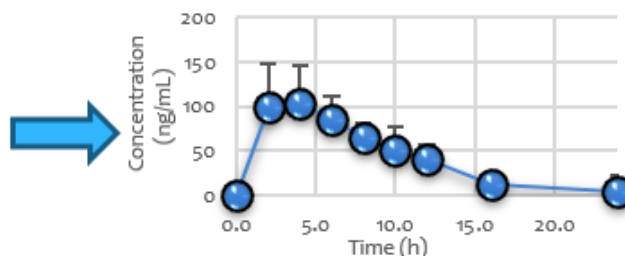
Evaluation of Drug Interactions with Sunscreen Active Ingredients

Percutaneously absorbed sunscreen active ingredients 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.



Sunscreen Clinical Study

Sunscreen products are widely used, and exposure to these chemical compounds could lead to unknown adverse reactions. Therefore, a clinical study is being performed to assess the systemic exposure of the sunscreen active ingredients under maximal usage conditions and determine the pharmacokinetics of those active ingredients.

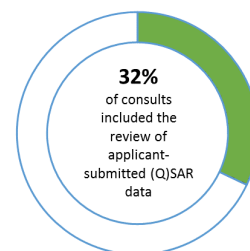
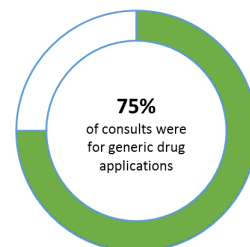
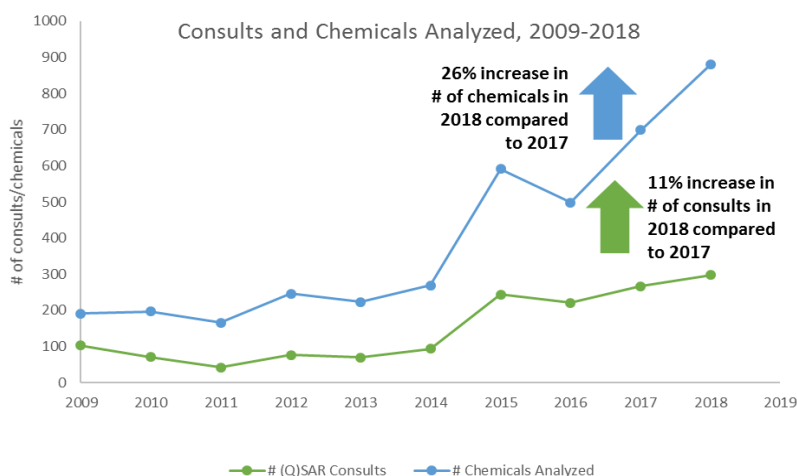


ClinicalTrials.gov Identifier: [NCT03582215](https://clinicaltrials.gov/ct2/show/study/NCT03582215)

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 15 chemical structures per week.



2018 Accomplishments

- ◆ Rolled-out updated models for bacterial mutagenicity, reproductive and developmental toxicity, and drug-induced liver injury
- ◆ Co-authored “Teach Tool” for reviewers on evaluating applicant-submitted (Q)SAR data
- ◆ Co-authored three external publications on best practices

Amberg, et al. *Regul Toxicol Pharmacol.* 2018. doi: [10.1016/j.yrtph.2018.12.007](https://doi.org/10.1016/j.yrtph.2018.12.007).

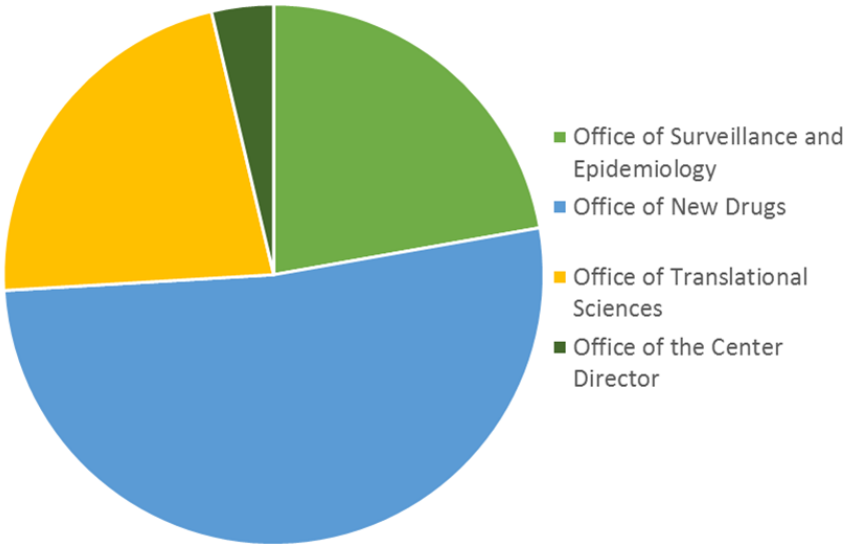
Hsu, et al. *Regul Toxicol Pharmacol.* 2018. doi: [10.1016/j.yrtph.2018.09.026](https://doi.org/10.1016/j.yrtph.2018.09.026).

Amberg, et al. *Mutagenesis.* 2018. doi: [10.1093/mutage/gev020](https://doi.org/10.1093/mutage/gev020).

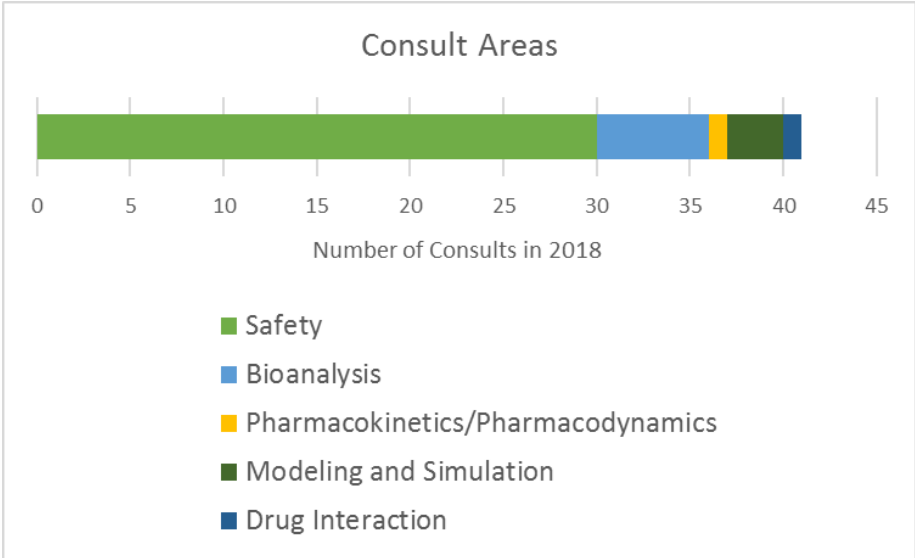
CONSULTS

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.

Consults are provided for multiple offices within the FDA.



DARS develops tools, standards, and approaches to answer many questions about drug safety, bioanalytical approaches, pharmacokinetic and pharmacodynamic interactions, and other complex issues arising from regulatory review.



COMMUNICATIONS

Publications, Presentations, and Reviews

41

Internal and External Posters

57

Publications

54

Internal and External Presentations

- DARS Expert Journal Reviews**
- American Journal of Cardiology
 - American Journal of Pathology
 - Annals of Emergency Medicine
 - Annals of Internal Medicine
 - Annals of Medicine
 - Cancer Chemotherapy and Pharmacology
 - Cellular and Molecular Bioengineering
 - Cellular Physiology and Biochemistry, Circulation
 - Clinical Pharmacology and Therapeutics
 - Digestive Disease
 - Drug Safety
 - Europace
 - International Journal of Cardiovascular Imaging
 - International Journal of Medical Sciences
 - International Journal of Women’s Health
 - Journal of Pharmaceutical Sciences
 - Journal of the American Medical Association: Internal Medicine
 - Journal of Applied Toxicology
 - Journal of Cellular Physiology
 - Journal of Cheminformatics
 - Journal of Clinical Medicine
 - Journal of Electrocardiology
 - Journal of Pharmacological and Toxicological Methods
 - Journal of the American Medical Informatics Association
 - Journal of Physiology
 - Journal of the Pancreas
 - Journal of Women’s Health
 - Medical Letter
 - Molecular Medicine Reports
 - Mutagenesis
 - Nature Protocols
 - Pharmacotherapy
 - Toxicology Letters
 - Xenobiotica

DARS also provides expert reviews for multiple internal and external efforts, including journals and grants.



SUMMARY

DARS Multidisciplinary Staff and Expertise

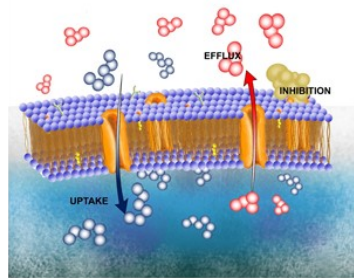
Veterinarians

Microbiologists

Toxicologists

Pharmacologists

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

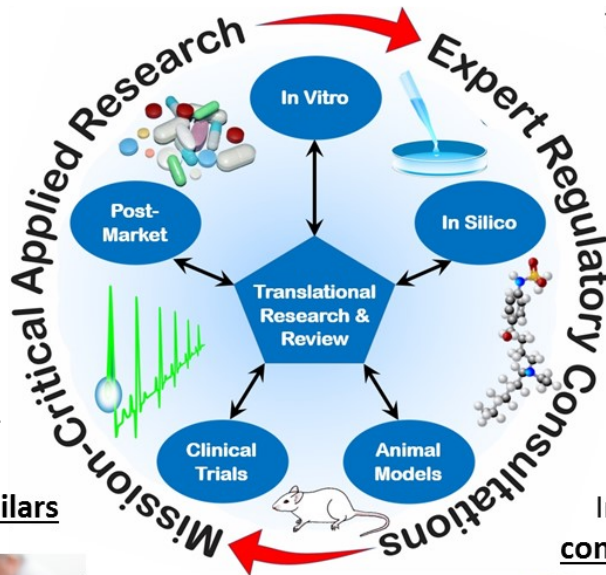
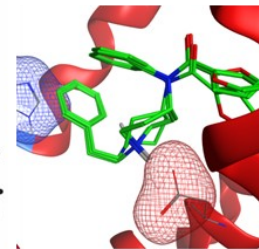


Computational Biologists

Integrated mechanistic assessment for postmarket safety signals



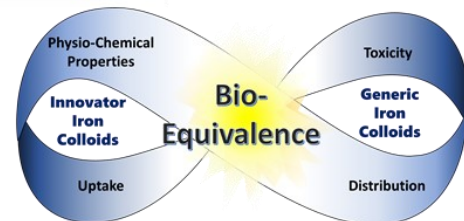
Computational modeling for drugs with abuse potential



Clinical studies for biomarkers for new drugs and biosimilars



In vivo models for complex generic drugs



Engineers

Physicians

Immunologists

Molecular/Cell Biologists

Inorganic Chemists



U.S. FOOD & DRUG
ADMINISTRATION

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