U.S. FOOD & DRUG ADMINISTRATION

Division of Applied Regulatory Science

Annual Report

2020

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

www.fda.gov

CONTENTS

Throughout this report, the following icons will be used to indicate the methodologies used for each research program:

Studies performed in the laboratory with cells in a test tube or dish

Studies performed with animal models

Studies performed with computational models

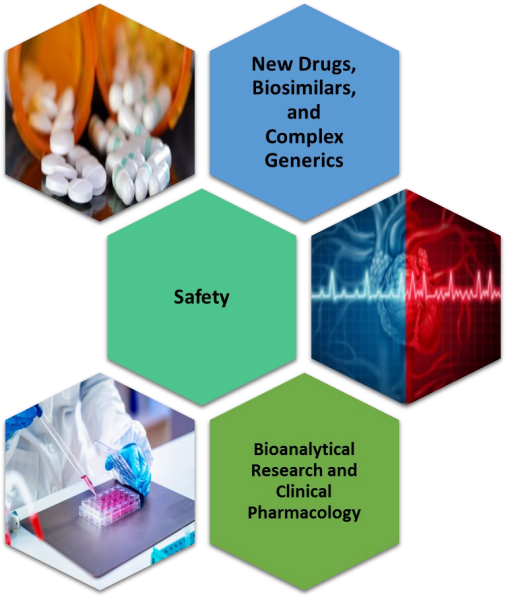
Prospective studies performed with people

Studies using patient health data or data routinely collected during delivery of health care

DIRECTOR'S MESSAGE

2020 was a challenging year. In addition to adjusting to new work environments related to the COVID-19 pandemic that involved 100% teleworking for some staff and laboratory work with new restrictions, DARS experienced the sudden loss of two highly valued team members. And yet, our multi-disciplinary team continued to come together and "step up to the plate" to advance high-priority mission-critical projects and take on new responsibilities throughout the year.

This year's annual report first provides overviews of our research as it relates to **1) efficacy, 2) safety and 3) clinical pharmacology**. We then highlight cross-cutting programs in cardiac safety, biosimilars and generics, and opioids, followed by the five translational research methodologies defined in circles on the prior page.



A major focus for the year was **advancing translational models and tools** into the drug review process. This included updating the international regulatory guidelines for cardiac safety and studying the reproducibility of microphysiological systems for use in drug development. We also studied novel computational modeling methods for diverse topics including COVID-19, opioids, organ toxicity and pediatric cancer.

DARS also **greatly expanded its clinical trials operations**, running three clinical trials related to streamlining biosimilars development and studying safety questions related to opioids and over-the-counter drugs. Finally, DARS provided **regulatory consults/reviews on critical public health and regulatory questions** related to investigational drugs for COVID-19, expanding the approval of drugs for rare diseases based on *in vitro* efficacy data and many additional topics.

Thank you to the entire DARS team and all of our collaborators.

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

RESEARCH OVERVIEW

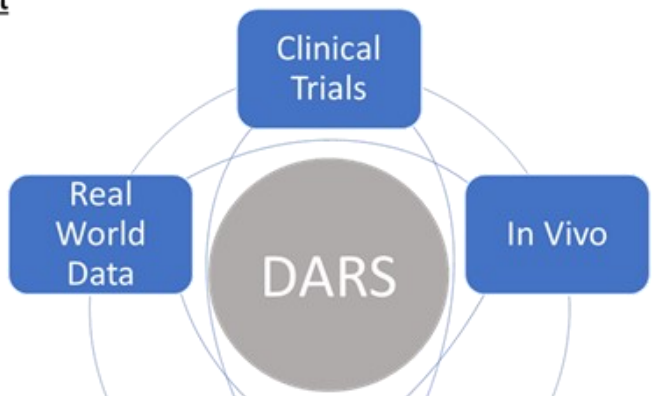
The Division of Applied Regulatory Science (DARS) was created to move new science into the drug review process and close the gap between scientific innovation and drug review.

The Division's multidisciplinary staff form teams "on-demand" to perform mission-critical research and expert regulatory review consultations. Questions from these consults often become the foundation for research to fill regulatory knowledge gaps, enhance drug development, and facilitate review.

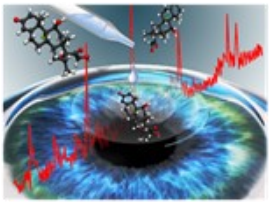
Examples of Applied Translational Research in DARS

Clinical studies for biomarkers for **biosimilars**

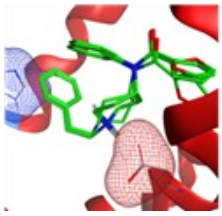
Mechanistic and structural assessment for **postmarket** safety signals



In vivo and in vitro models for **complex generics**



Computational and in vitro modeling for **drugs with abuse potential**



In vitro toxicity evaluation for **new drugs**

RESEARCH OVERVIEW

New Drug Efficacy and Biosimilar/ Complex Generics Pivotal Studies

DARS performs studies to characterize the performance of new translational models and tools to assess the efficacy or performance of new drugs, biosimilars and complex generics.

New Drug Efficacy

- ***In Vitro***

  DARS provides expert review on study quality and results when novel methodologies are used to support expanding the indications of drugs to genetic variants not studied in clinical trials. This has included treatments for the rare diseases cystic fibrosis and Fabry Disease. Additionally, DARS has developed an *in vitro* hollow fiber method to study the effect of drug combinations to reduce the emergence of antibiotic-resistant bacteria.

- ***In Silico***

  Computational efforts, including machine learning and text-mining, are ongoing to identify potential synergies between COVID-19 drugs and to identify oncology drugs that should be studied for use in children.

- **Clinical Trials**

  DARS evaluates clinical pharmacodynamic biomarkers that could be used to assess the rapid onset-of-action for new opioid antagonists, routes of administration or formulations to address overdose deaths from opioids.

Biosimilars and Complex Generic Pivotal Studies

- **Clinical Trials**

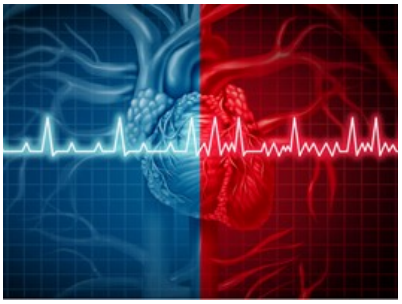
  Three clinical trials are underway to inform standards for pharmacodynamic biomarkers to speed and reduce the cost of biosimilar development.

- ***In Vivo***

  DARS charaterizes novel approaches using animal models to predict and assess bioequivalence and biosimilarity to enhance generic and biosimilar product development and review.

RESEARCH OVERVIEW

Safety Research

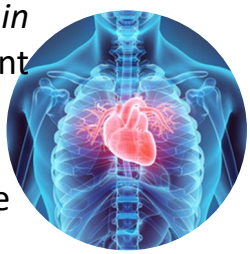


DARS performs research on both pre- and post-market drug safety issues and questions.

This includes studying, validating and implementing new safety methodologies, such as novel *in vitro* and *in silico* methods, that can be applied to all new drugs.

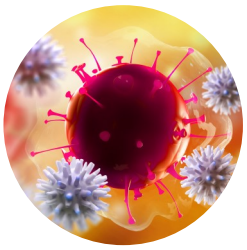
Cardiac Safety

- ***In Vitro*, *In Silico* and Clinical Trials — Proarrhythmia**
  DARS leads research across all domains of the Comprehensive *in vitro* Proarrhythmia Assay initiative and is working to implement changes through updated ICH Guidelines.
- ***In Vitro* and *In Silico* — Structural and Contractility Toxicity**
  DARS uses microphysiological systems and artificial intelligence to help predict cardiovascular effects of drugs.
- ***In Silico***
  A quantitative structure-activity relationship model is being developed to predict multiple cardiac toxicity endpoints.



Immune System Safety

- ***In Vivo***
  DARS studies the use of a humanized mouse model to predict immune-mediated adverse effects of biologics.



Neurotoxicity

- ***In Silico***
  DARS develops multiple predictive tools for neurotoxicity, including blood-brain barrier penetration, activity at vesicular monoamine transporter 2, and PHASE, a computational approach to identify a compound's risk to public health.

RESEARCH OVERVIEW

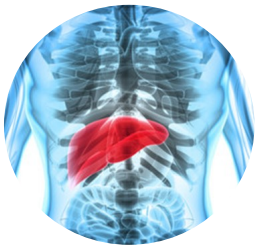
Safety Research

Respiratory Safety

- ***In Vivo* and Clinical Trials**

  Multiple nonclinical *in vivo* studies and clinical trials are evaluating the interactions between opioids and other sedative psychotropic drugs on respiratory depression.

Liver Safety

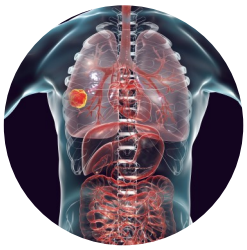


- ***In Vitro***

  Induced pluripotent stem cells and microphysiological systems are being evaluated for use in drug development.

- ***In Vivo***

  Humanized mouse models with a human liver are being studied for their ability to predict the risk of drug-induced liver injury in people.

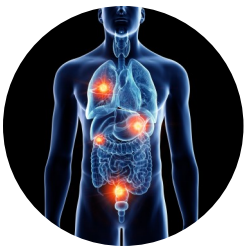


Cancer Risk

- ***In Silico***

  Quantitative structure-activity relationship models are utilized to predict carcinogenicity and mutagenicity risk.

Multi-organ Toxicity



- ***In Silico***

  Machine learning methods are being studied for their ability to predict risk of adverse events.

- **Real-World Data**

  DARS leverages real-world data to recommend updates to drug labels.

- ***In Vitro***

  An interconnected heart-liver microphysiological system is being assessed for performance and reproducibility in predicting dual organ or metabolism-dependent toxicity.

- ***In Vitro/In Silico***

  In vitro assay data submitted with drug applications are analyzed and placed into a user-friendly database.

RESEARCH OVERVIEW

DARS has extensive capabilities to quantify small and large molecule drugs and biomarkers in biological samples from laboratory studies and clinical trials.

DARS models pharmacokinetics and pharmacodynamics from DARS-run laboratory studies and clinical trials.

Systemic Exposure to Widely-Used Drugs

- **Clinical Trials**

  DARS led clinical trials to evaluate systemic exposure to the active ingredients in sunscreen. DARS is also studying whether *N*-nitrosodimethylamine (NDMA) (a probable human carcinogen) in human urine increases after ranitidine administration. Results inform the need for further studies or other regulatory action.

Drug Interactions

- **General assessments**

  Novel methods, including iPSC hepatocytes and microphysiological systems, as well as traditional methods are used to evaluate drug-drug interactions.

- **Sunscreen**

  DARS conducts sunscreen absorption clinical trials and is investigating the potential for drug interactions with sunscreen active ingredients *in vitro.*

- **Opioids and sedative psychotropic drugs**

  DARS conducts multiple nonclinical and clinical studies on the interaction between opioids and psychotropic drugs and effects on respiratory depression.

Additional Areas

- **Blood Brain Barrier**

  An *in silico* model is being developed to predict whether a drug will cross the blood brain barrier, which will inform neurotoxicity evaluation.

- **Immunogenicity**

  DARS utilizes *in vitro* and *in vivo* techniques to assess the immunogenic potential of generic peptide products.

PROGRAM HIGHLIGHTS

Cardiac Safety Research Program

DARS leads research, in collaboration with external consortia, to overhaul the approach to assessing the risk of abnormal heart rhythms for all new drugs and update regulatory guidelines.

- Research on *in vitro* assay standards and best practices, development and validation of *in vitro*/*in silico* proarrhythmia models, and characterization of clinical biomarkers.

Outcomes:

25 **Recent Publications.** Additionally, a CDER Impact Story was published in March 2020.

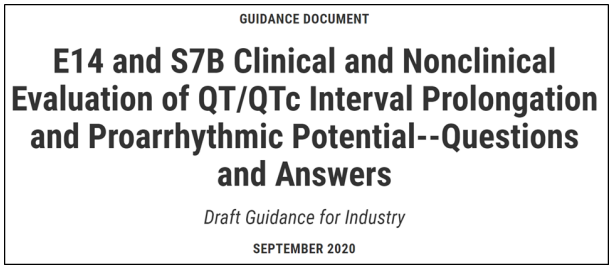
3 **FDA-sponsored prospective clinical trials** to assess cardiac safety biomarkers

5 **Public think tanks** and **collaborative workshops**

3 **Communications from the International Council for Harmonisation (ICH)**, including a Draft Guideline, concept paper, and webinar. Further, DARS served as rapporteur (lead) for ICH guidelines S7B and E14 updates.

Additionally:

- In 2017, an FDA Advisory Committee endorsed the proposed strategy and validation approach
- In 2021, ICH released a new ICH Draft Guideline


GUIDANCE DOCUMENT

E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential--Questions and Answers

Draft Guidance for Industry

SEPTEMBER 2020

January 2021

PROGRAM HIGHLIGHTS

Biosimilars and Complex Generics Research Program

DARS performs research to advance novel drug development tools to streamline biosimilar and complex generic development, including:

- Clinical trials to characterize biomarkers for biosimilar development
- In vivo studies to characterize the acceptability of surrogate markers of bioequivalence
- Suitability of bioassays for PEGylated biosimilar products

Pharmacodynamic (PD) Biomarkers for Biosimilar Approval

To help patients realize the benefit of a robust, competitive market for biosimilar products, FDA is focused on improving the efficiency of biosimilar development (FDA's Biosimilars Action Plan). In support of this:

- **DARS is conducting research to inform FDA's thinking on the use of PD biomarkers to reduce the need for comparative clinical efficacy studies**.

This includes performing clinical studies to characterize known biomarkers and explore the use of technologies to identify new biomarkers or assess multiple biomarkers simultaneously (e.g. proteomics and small-RNA biomarkers). Studies include biologics with:

- PD biomarkers used as a surrogate end point for the reference product
- Known PD biomarkers tied to the mechanism of action but not used as a surrogate end point for the reference product
- No existing well-characterized PD biomarker(s) for the reference product

This research will further define key characteristics for PD biomarkers to reduce the need for comparative clinical efficacy studies.

3 FDA-sponsored clinical trials on six drugs are being performed to characterize biomarkers for biosimilar development.

1 Recent Summary Publication

PROGRAM HIGHLIGHTS

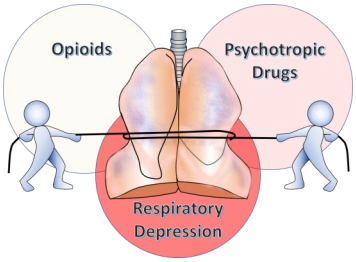
Opioids Research Program

To address the growing opioid crisis and in response to FDA's Opioid Action Plan, DARS developed a multi-pronged approach to evaluate the safety of using opioids in combination with other prescription sedative psychotropic drugs and to evaluate how much naloxone is needed to rescue patients with opioid overdoses:

- *In silico* and *in vitro* models to evaluate naloxone dosing
- *In vivo* models to identify drug interactions
- Clinical trials to assess translation to humans

Opioids and Sedative Psychotropic Drug Interactions

Benzodiazepines interact with opioids to increase the risk of respiratory depression. It is unclear whether other psychotropic drugs cause a similar effect. DARS is performing nonclinical *in vivo* studies and clinical trials to evaluate the interaction between sedative psychotropic drugs and opioids on respiratory depression. This will **inform the need for safety communications and labeling updates**.



1 Recent Publication. Additionally, a CDER Impact Story was published in August 2018.

1 FDA-sponsored clinical trial to evaluate the respiratory effect of the co-administration of opioids and psychotropic drugs

Pharmacokinetic (PK) - Pharmacodynamic (PD) Models to Predict Naloxone Dosing Requirements for Highly Potent Opioids

DARS developed a new approach using *in vitro* opioid-receptor assays and *in silico* modeling to evaluate naloxone dosing regimens to reverse overdoses from highly potent opioids (e.g. fentanyl derivatives) when clinical data does not exist. The results will **inform on the need for new naloxone dosing strategies in the community setting**.

PROGRAM HIGHLIGHTS

Clinical Trials and Related Programs

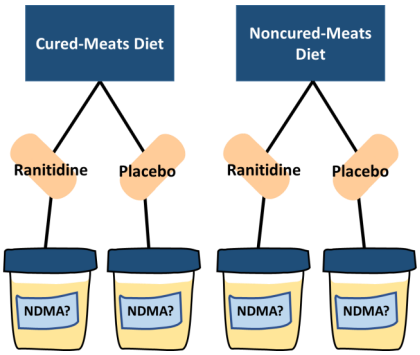
In Vitro
In Vivo
In Silico
Clinical Trials
Real World Data

DARS greatly expanded its capability to run prospective clinical trials to address critical regulatory, drug development and public health questions. This informs review, guidance, labeling, and safety communications. Clinical trials include:

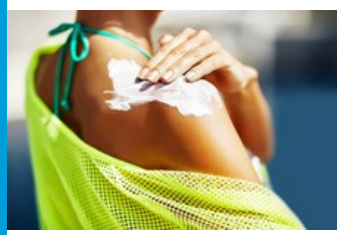
- Characterization of biomarkers to streamline biosimilar development
- Interaction between opioids and sedative psychotropic drugs
- Exposure to NDMA (probable human carcinogen) after taking ranitidine
- Systemic absorption of and exposure to sunscreen active ingredients
- Cardiac safety biomarkers to be applied in phase 1 clinical trials

Exposure to NDMA Following Ranitidine

NDMA, a probable carcinogen, is contained in foods and has been identified as an impurity in some drugs. It is unclear if NDMA can form in the body following ranitidine administration. A clinical trial is evaluating the urinary excretion of NDMA after ranitidine administration compared to placebo.



Systemic Absorption of Sunscreen



DARS ran two clinical trials to assess the systemic exposure of sunscreen active ingredients. Ongoing work is assessing the potential for drug-drug interactions *in vitro* and the identification of metabolites to the sunscreen active ingredients.

3 Recent Publications, including the most-read JAMA article of 2019.

Since the first clinical trial was published in May 2019:

184,983 views

106 citations

355 news stories

Additional statistics

PROGRAM HIGHLIGHTS

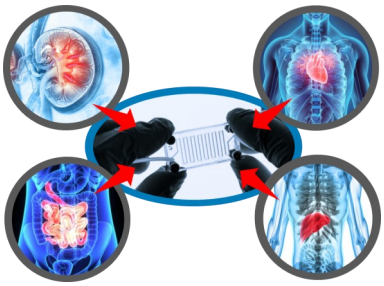
In Vitro Models Research Program

In Vitro
In Vivo
In Silico
Clinical Trials
Real World Data

DARS is evaluating multiple complex *in vitro* models and tools to establish standards, best practices, and guidance for use in drug development and regulatory review including:

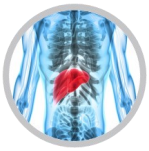
- Hollow fiber model for antibiotic resistance
- Microphysiological models to evaluate drug safety
- Induced pluripotent stem cells (iPSC) for safety and metabolism
- Cell-based models for PK/PD assessments

Microphysiological Systems (MPS) for Drug Development

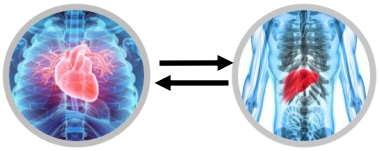


Microphysiological systems, or "organ-on-a-chip", demonstrate great potential for use in drug development due to their ability to more closely mimic human systems compared to traditional *in vitro* models. Three models are being evaluated in DARS for their **potential use in regulatory evaluation of drugs for safety and clinical pharmacology, including to replace clinical trials**.

Heart: Comparative study of cardiac MPS to evaluate their robustness and reliability relative to other traditional cell culture platforms and when different cell lines are used.



Liver: *In vitro* study to characterize the reproducibility of results and the use of a liver MPS for quantifying drug metabolism, intracellular accumulation and evaluating drug toxic effects.



Interconnected Heart-Liver: Evaluation of the potential of a heart-liver interconnected MPS for predicting dual cardiac and hepatic drug toxicity and to model cardiac toxicity that depends on liver metabolism.

2 Recent Publications. Additionally, a CDER Impact Story was published in October 2018.

3 **Microphysiological systems** under evaluation; multiple additional planned.

PROGRAM HIGHLIGHTS

In Vivo Models Research Program

In Vitro
In Vivo
In Silico
Clinical Trials
Real World Data

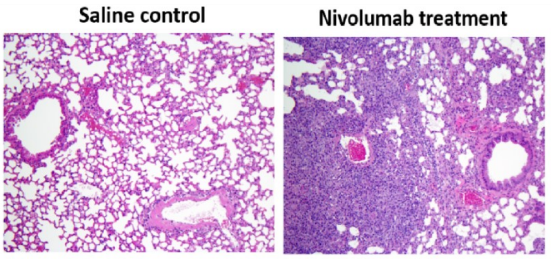
DARS is evaluating *in vivo* models with the potential for improved human predictivity to address safety concerns and assess efficacy. Current *in vivo* models include:

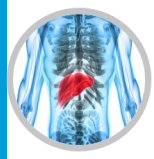
- Humanized mouse models for evaluating hepatotoxicity and immunotoxicity in drug development
- Systematic approaches to assessing bioequivalence for locally active products using generic ocular implants
- Immunogenic potential of generic peptides
- Validation of model-informed drug development approaches for slow-release risperidone injection generics

Humanized Mouse Models

DARS developed "humanized mice", which is an *in vivo* model that closely mimics the human hepatic and immune systems. This model can be used to provide better **insight into human metabolism and toxicity** than traditional models during drug development and **support biomarker development**.

Checkpoint Inhibitor Pneumonitis





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

Immune: Humanized mice are used to evaluate the immune-mediated effects of biologics, which can result in poor efficacy or life-threatening reactions.

5 Recent Publications

PROGRAM HIGHLIGHTS

In Silico Models Research Program

DARS has a variety of *in silico* models to predict drug efficacy and safety. Models DARS is currently developing include:

- (Q)SAR models for multiple endpoints
- General adverse event prediction using machine learning
- Repurposing an influenza model to predict efficacious drug combinations for COVID-19
- Best practices for quantitative systems pharmacology in new drug review
- Identification of the naloxone dosage needed to reverse opioid-induced respiratory depression

(Quantitative) Structure-Activity Relationship Models

(Quantitative) Structure-Activity Relationship [(Q)SAR] models make predictions for toxicity endpoints based on chemical structure. These models can be used both pre-market and post-market for drugs and related compounds, including excipients, metabolites, and impurities, to **evaluate the potential for adverse events and support labeling**. In 2020, three model endpoints were developed:

Public Health: Combined with other analyses, such as target prediction and molecular docking, (Q)SAR principles were applied to predict the risk of a chemical to public health, using kratom as a case study.

Blood-Brain Barrier: To assist in assessment of neurotoxicity and public health risk, a (Q)SAR model was developed to predict a compound's permeability of the blood-brain barrier.

Heart: A (Q)SAR model was built in 2006 to predict cardiotoxicity. The model is being updated with new data and endpoints to identify new chemical structures and cardiac events.

9 Recent Publications

4 **Model endpoints** under development

PROGRAM HIGHLIGHTS

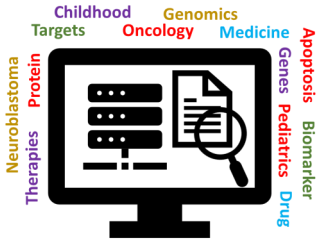
Informatics and Real-World Data Research Program

DARS is combining *in vitro, in vivo,* and real-world data to inform guidance, improve labeling, and enhance regulatory decision making:

- Evaluating data across labeling, studies, post-market reports, and other sources to make recommendations for improved labeling structure, language, and regulatory review practices
- Analyzing and synthesizing *in vitro* safety pharmacology data across all new drug development programs to standardize data submission and predict drug safety
- Development of a text-mining algorithm to support review efforts for pediatric oncology

Text-Mining for Pediatric Cancer

In collaboration with review staff in the Offices of Clinical Pharmacology and New Drugs, DARS is developing text-mining algorithms to identify targets that are associated with pediatric cancer. These tools are being used to **inform development of the Pediatric Molecular Target List and pediatric study plan reviews**, in accordance with the Research to Accelerate Cures and Equity (RACE) Act.



4 **Text-mining algorithms** under development, with additional algorithms planned

Overdosage Labeling

DARS utilizes manual and automated review of Section 10, Overdosage, to identify outdated recommendations. New language is proposed to relevant review divisions with justification and source documentation.

2 **Drug labels** will be updated

ENGAGEMENT

37 Publications

46 Presentations

25 Posters

Expert review provided for

4

intramural and extramural funding programs

34 Collaboration Agreements

Across 12 states and 4 countries

DARS provided expert reviews for over 20 journals, including:

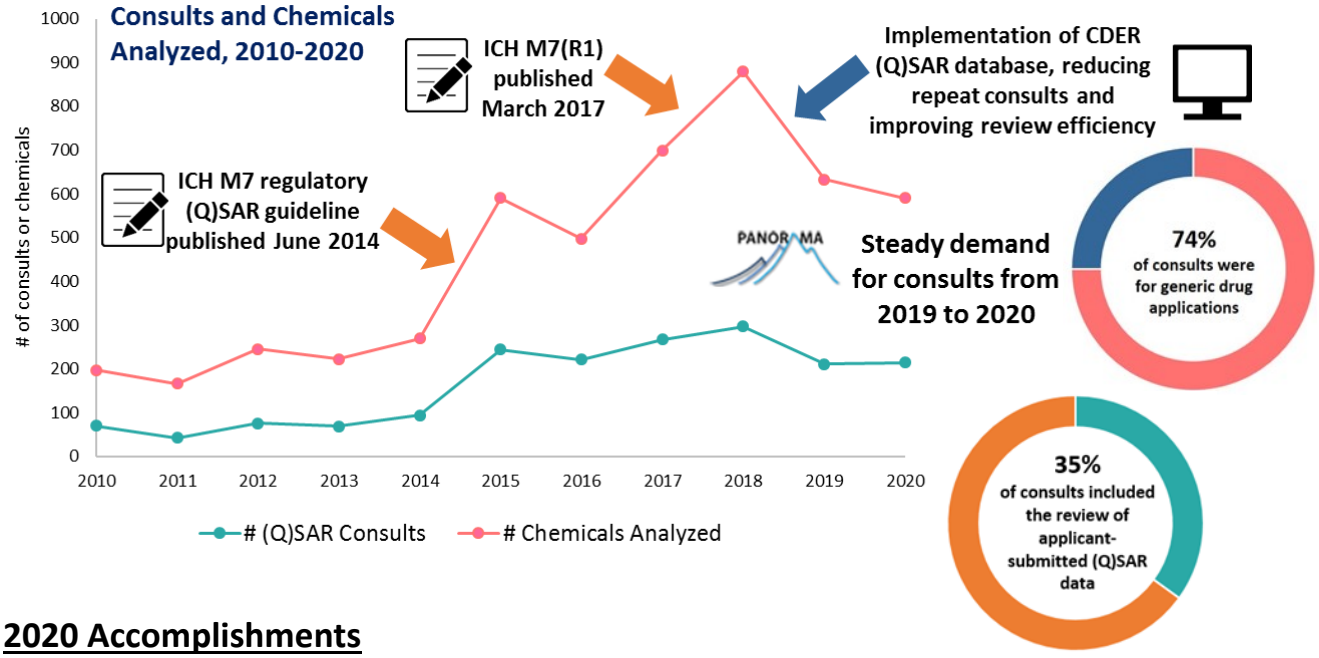
- Clinical Pharmacology and Therapeutics
- Clinical Cancer Research
- Journal of Pharmaceutical Sciences
- JAMA Dermatology
- Journal of Cheminformatics
- Antibiotics
- Chemical Research in Toxicology
- Pharmaceutical Research
- Journal of Pharmaceutical Analysis
- Clinical and Translational Science
- PLoS ONE
- Journal of Bioequivalence Studies

January 2021

(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.



2020 Accomplishments

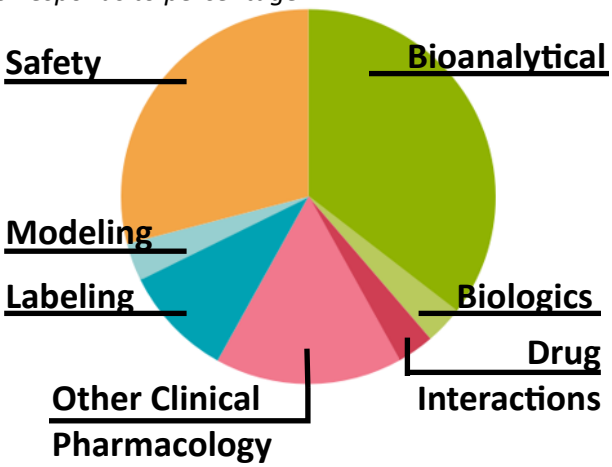
- **April:** Launched Panorama-based (Q)SAR consultation process to support new drug application review (IND and NDA)
- **May**: FDA Impact Story published online showcasing our work on drug impurities using (Q)SAR modeling
- **September**: Received CDER Honor Award for design and implementation of new (Q)SAR Consult Database
- Co-authored two publications on new models and best practices:

  Yoo, et al. Regul Toxicol Pharmacol. 2020, 113:104620.

  Hasselgren, et al. Regul Toxicol Pharmacol. 2020, 104:104807.

DIVISIONAL CONSULTS

Consults in each of seven topic areas. Size of slices corresponds to percentage.



DARS performs expert regulatory review consultations that combine a critical review of existing knowledge, computational assessments, laboratory studies, and translational analysis of preclinical, clinical trial and post-market data.

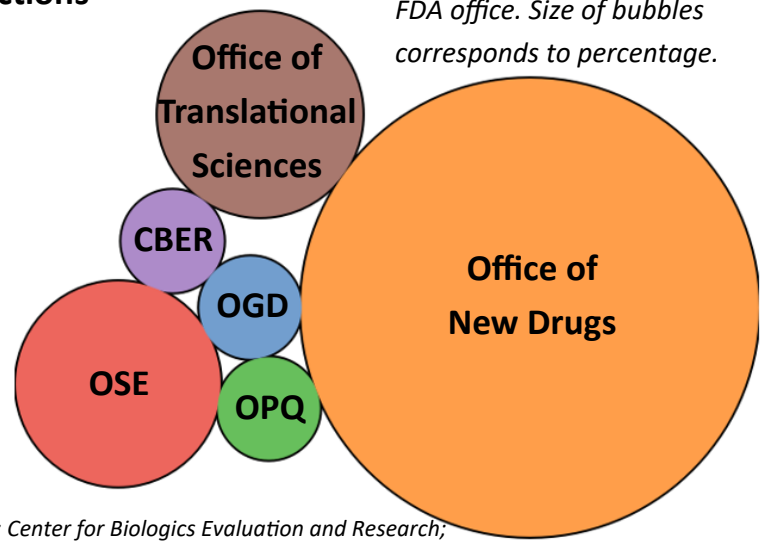
31

Consults Completed

5

Review Team Contributions

Consults completed for each FDA office. Size of bubbles corresponds to percentage.



CBER: Center for Biologics Evaluation and Research; OGD: Office of Generic Drugs; OPQ: Office of Pharmaceutical Quality; OSE: Office of Surveillance and Epidemiology

Remdesivir Safety

DARS performed a review of renal and hepatic toxicity associated with remdesivir. DARS found that remdesivir and its metabolites were structurally similar to drugs that are associated with renal and hepatic toxicity. Potential risk of these events is now contained in remdesivir's labeling.

Efficacy for Cystic Fibrosis Drugs

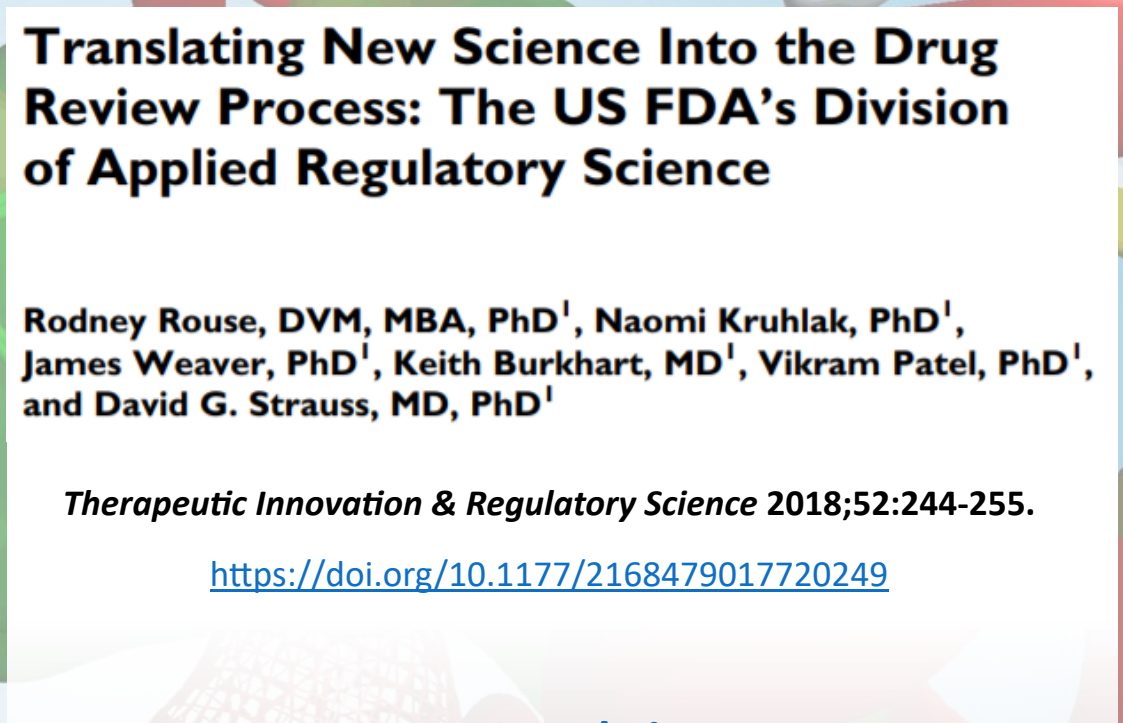
DARS led the review of *in vitro* data that served as the primary evidence of effectiveness to expand the approval of three cystic fibrosis drugs to hundreds of rare genetic variants that were not studied in clinical trials. DARS' review included re-analysis of raw data and careful quality control assessment.

Other Contributions

DARS led or participated on multiple review teams, working groups, and task forces, including teams focusing on COVID-19 safety issues and approvals and vaping-associated lung injury.

ENGAGEMENT

Want to Learn More About DARS?



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

Rodney Rouse, DVM, MBA, PhD[1], Naomi Kruhlak, PhD[1], James Weaver, PhD[1], Keith Burkhart, MD[1], Vikram Patel, PhD[1], and David G. Strauss, MD, PhD[1]

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

https://doi.org/10.1177/2168479017720249

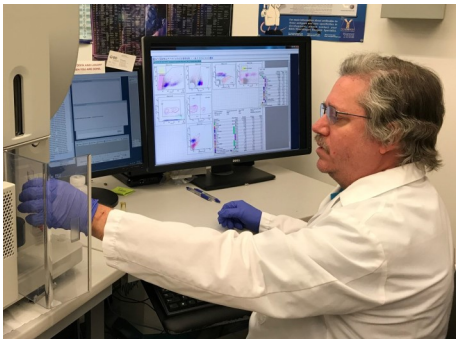
DARS Website

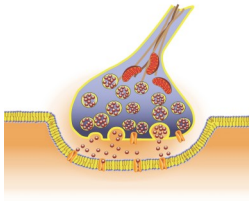
Contact: Rodney.Rouse@fda.hhs.gov

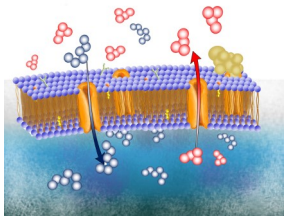
IN MEMORIAM

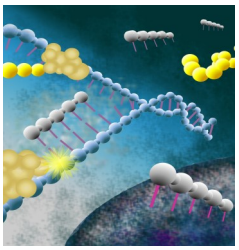
In 2020, DARS lost two of our valued team members.

Alan Knapton was a treasured scientist, artist, and friend in DARS. As a mentor who trained numerous fellows and scientists over his 30-year career with the government, he was always willing to share his knowledge on a wide range of topics including vascular, heart, liver, and immune system toxicity. Additionally, as a gifted artist, his drawings were often featured in DARS' annual reports as well as multiple presentations. Alan's talents, skills, and positivity will be greatly missed.









A Sample of Alan's Artwork

Alan's Publications

Neil Hartman was a cherished inventor, scientist, and friend in DARS. Neil worked for over 25 years at FDA on a multitude of topics including transplant rejection drugs, HIV therapies, methemoglobinemia, and liver metabolism. Before retiring in September 2020, one of Neil's final contributions was leading DARS' review of remdesivir's adverse events (pg. 19). Besides his scientific accomplishments, Neil will especially be remembered by his ability to see humor in all situations and his fantastic sock collection. Neil's expertise and quick wit will be greatly missed.

Neil's Publications

Neil's Patent

Neil on the winning team at a DARS teambuilding retreat

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