U.S. FOOD & DRUG ADMINISTRATION

Office of Translational Sciences | Office of Clinical Pharmacology

Division of Applied Regulatory Science

2022 Annual Report

January 2023

www.fda.gov

Table of Contents

3 Director's Message
4 DARS by the Numbers
5 Applied Research Overview
6 Responding to Critical Regulatory Review and Public Health Problems
10 Prescription Drugs Overview
14 Generic Drugs and Biosimilars Overview
17 Policy, Guidance, & Review
18 Regulatory Consults and Review
19 Contact Us

Message from the Director

The Division of Applied Regulatory Science (DARS) is uniquely positioned to move new science into the FDA regulatory process and address emergent regulatory and public health questions. To do so, DARS' multidisciplinary staff engages stakeholders to conduct mission-critical applied laboratory, computational, and clinical research. DARS is frequently engaged by FDA colleagues and senior leadership to address some of the Agency's largest challenges.

In 2022, DARS staff led research and review activities to address multiple complex regulatory issues, including the safety and efficacy of COVID-19 therapies, safe use of prescription opioids, and treatment of opioid overdose as well as advancing the use of biomarkers for biosimilar drug development. In addition, DARS established programs to advance drug development for rare diseases and use of alternative methods to animal testing.

DARS staff continued to develop laboratory, computational and clinical drug development tools to advance regulatory science and policy at FDA and inform international standards. For example, DARS leads a collaboration of international stakeholders developing new criteria, standards and best practices for using a combination of laboratory, computational and clinical methods in an International Council of Harmonisation (ICH) regulatory guideline for cardiac safety assessment.

I am honored to be a part of DARS' dedicated team of scientists and extremely proud of all they have accomplished in advancing public health in 2022. Again this year, thank you to all the DARS staff and our collaborators and stakeholders within and outside of FDA.

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

DARS by the Numbers

DARS demonstrated continued success in 2022 despite the challenges brought on by the pandemic.

52 Applied research projects

24 Manuscripts published

48 Presentations delivered

29 Posters

39 Collaborations across 6 countries

19 Research Collaboration Agreements

2 Cooperative Research and Development Agreements

18 Material Transfer Agreements

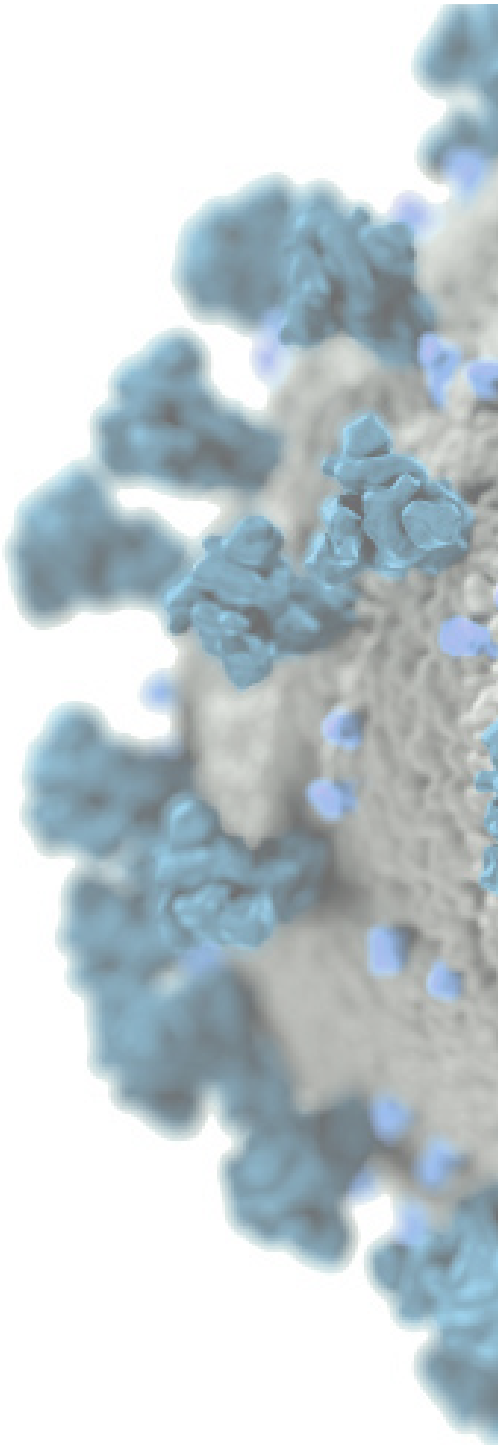
Applied Research Overview

The FDA's Division of Applied Regulatory Science (DARS) moves new science into the drug review process and addresses emergent regulatory and public health questions for the Agency. By forming interdisciplinary teams, DARS conducts mission-critical research to provide answers to scientific questions and solutions to regulatory challenges. DARS is staffed by experts with decades of experience 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.

DARS forms synergies by pulling together scientists and experts from diverse backgrounds to collaborate in tackling some of the most complex challenges facing FDA. DARS is tasked with wide ranging issues that encompass regulatory science; DARS, in turn, helps the Agency solve these challenges. The select projects in the following pages of this report demonstrate the impact of DARS on patients, the pharmaceutical industry, and fellow regulators.

Responding to Critical Regulatory and Public Health Problems

DARS applied research capabilities and activities empower the agency to respond rapidly to emergent regulatory and public health questions regarding the products it regulates. This includes responding to the COVID-19 pandemic and addressing the misuse and abuse of opioid drugs.



COVID-19

MECHANISTIC COVID-19 MODELING

DARS has modified its previously developed influenza mechanistic model to COVID-19. Published in Clinical Pharmacology & Therapeutics, this work demonstrates the possibility of quantitatively predicting clinical outcome based on nonclinical data and a mechanistic understanding of the disease. This provides a modularized framework to aid in candidate drug selection and clinical trial design for COVID-19 therapeutics.

FDA ACMT COVID-19 TOXIC (FACT) PHARMACOVIGILANCE PROJECT SUB-REGISTRY

In response to the COVID-19 pandemic, DARS and the Office of Surveillance and Epidemiology contracted with ACMT's ToxIC to establish the FACT Pharmacovigilance Project Sub-registry to leverage the existing capabilities of the ToxIC registry as a surveillance tool to identify emerging safety issues associated with drugs to treat or prevent COVID-19. FACT has provided valuable safety information on these products. A manuscript on ivermectin, a product that has not been shown to be effective in COVID-19, has been published, and additional manuscripts are in development.

Drugs of Addiction and Abuse

Prescription opioids are powerful pain-reducing medications that have both benefits as well as serious risks. One of FDA's highest priorities is advancing efforts to address the crisis of misuse and abuse of opioid drugs.

OPIOIDS, DRUG INTERACTIONS AND RESPIRATORY DEPRESSION

DARS developed and used a nonclinical in vivo model to study the effect of 14 psychotropic medications on breathing when given alone and in combination with an opioid. Study results helped design a DARS-led clinical trial to assess whether combining certain drugs with the opioid oxycodone, compared to oxycodone alone, decreased ventilation under higher carbon dioxide conditions. Compared to oxycodone alone, the selective serotonin reuptake inhibitor (SSRI) paroxetine in combination with oxycodone decreased ventilation.

FDA has initiated a separate clinical study to better understand if paroxetine's effect is observed with longer-term dosing and if similar effects are observed with other SSRIs. Additionally, findings from this study serve as a proof-of-concept of how this methodology could be used in the future to evaluate the effects of study drugs alone or in combination with other drugs on ventilation.

Based on results from the clinical trials, pharmacokinetic and pharmacodynamic (PK-PD) modeling was used to improve understanding of ventilation and pupillometry changes of midazolam, paroxetine and quetiapine with oxycodone compared to oxycodone alone.

Relevant publications

Florian et al. JAMA 2022, 328(14):1405-14.

Xu et al. Clin Transl Sci 2021, 14(6):2208-19.

Clinicaltrials.gov links for ongoing clinical trials

- NCT05338632
- NCT05470465

OPTIMIZING OPIOID REVERSAL AGENTS FOR USE IN A COMMUNITY SETTING

Many opioid overdose deaths are attributable to the synthetic opioid fentanyl. DARS is conducting multiple studies on opioid reversal agents and strategies, including:

- DARS, in collaboration with the University of Maryland, has applied an advanced molecular dynamics method called metadynamics to elucidate the dissociation mechanism of fentanyl and its analogs to calculate the residence times at the mu-opioid receptor. This new method was also used to predict the relative dissociation time of a newly identified opioid that emerged from illegal markets, helping to inform overdose prevention strategy.

- Combined cellular and computer modeling studies for fentanyl and multiple fentanyl derivatives to predict the amount of naloxone required to rescue patients from overdoses. This work has resulted in a published translational model that can evaluate the effect of opioid overdose and naloxone dosing strategies on respiratory depression and cardiac arrest, which was recently used to support the approval of a new naloxone product.

- DARS has conducted a clinical trial with different administration schedules of intranasal naloxone to better understand its pharmacokinetics following repeat administration, which may be needed to reverse overdoses involving highly potent opioids. These trial findings have been combined with the translational model mentioned above to optimize naloxone dosing strategies in a community setting.

- DARS, in collaboration with Leiden University, is investigating changes in ventilation and pupillometry following coadministration of opioid agonists and opioid reversal agents. Data is being collected in both healthy volunteers and chronic opioid users, and study findings will help optimize the use of approved opioid reversal agents and to inform feasible and efficient clinical trials to bring new opioid reversal agents to the market.

Relevant publications

Mann et al. Clin Pharmacol Ther 2022, 112(5):1020-32.

Vo et al. Nature Commununications 2021, 12(1):984.

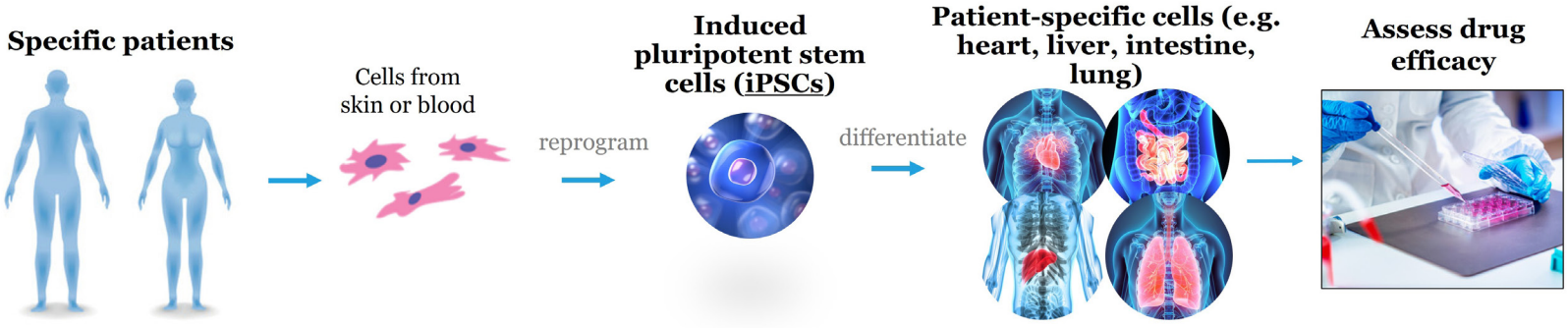
A SURVEILLANCE NETWORK FOR METHAMPHETAMINE AND OTHER STIMULANTS

Increasingly, opioids such as fentanyl are used with or found in combination with other substances such as methamphetamine, other stimulants, and even the veterinary sedative xylazine. As a result, DARS and Office of Surveillance and Epidemiology colleagues are evaluating clinical data such as fatality reports to inform the Agency's decision-making to better improve existing treatments and develop new antidotes. The clinical data comes from contracts with the American College of Medical Toxicology's Toxicology Investigator's Consortium and America's Poison Centers' National Poison Data System. The goal is to create a near real-time surveillance network to monitor the rapidly changing and increasingly complex illegal drug market. One key component is to obtain toxicologic analyses to monitor for novel psychoactive substances and correlate these to clinical outcomes.

Critical Regulatory Initiatives

RARE DISEASES

- Rare disease drug development is challenging because of the small number of patients and limited understanding of the disease's natural history.
- DARS is studying the use of in vitro cell-based approaches to assess the functional and biochemical response of rare disease variants in the presence of drug.
- DARS led the regulatory review and scientific framework development for using in vitro data to support drug efficacy in the absence of clinical trial data. This work led to the expansion of the approved patient populations for certain drugs for two rare diseases: cystic fibrosis and Fabry disease.
- Through further applied research, DARS seeks to broaden the applicability of these types of models.



ALTERNATIVE METHODS

- DARS is leading FDA efforts to advance the use of alternative methods (cell- and computer-based models) that have the potential to enhance safety and efficacy assessments and address the "3Rs" (replace, reduce and refine animal testing).
- DARS is working to fill information gaps with applied research to advance new policy and guidance in this area.
- This includes advancing standards, quality control criteria and best practices for different alternative methods technologies.

Prescription Drugs
Overview

DARS' multidisciplinary teams advance high-priority and mission critical projects to address the safe and effective use of prescription drug products. Through clinical trials, computational modeling, and laboratory-based models DARS studies critical public health issues, such as opioids and improving the safety assessment of new drugs.

Selected Prescription Drug Activities

IDENTIFYING MOLECULAR TARGETS FOR PEDIATRIC CANCER

DARS is developing natural language processing algorithms to identify molecular targets associated with pediatric cancer. These algorithms inform the development and maintenance of the Pediatric Molecular Target List and pediatric study plan reviews in accordance with the Research to Accelerate Cures and Equity (RACE) Act. DARS is also providing expertise to the Convening Experts in Oncology to Address Children's Health (COACH) initiative through the Foundation for the National Institutes of Health.

DRUG OVERDOSE LABELING

DARS is using natural language processing to identify information of interest from prescription drug labeling. Drugs from 11 drug classes highly associated with drug overdose fatalities are being evaluated with this tool to identify labeling with potentially outdated overdose treatment recommendations. Results will inform updates to the overdose section of drug labeling. Safety labeling changes for the selective serotonin reuptake inhibitors and benzodiazepines have included updates to Section 10 OVERDOSAGE of their labeling.

Antibiotic Resistance and Drug-Drug Interactions

ANTIBIOTIC RESISTANCE

DARS developed a novel hollow fiber cell-based method to measure the rate at which antibiotic resistance appears. This system is used along with human pharmacokinetic profiles to identify drug combinations that have the potential to reduce the development of resistance. Next-generation sequencing is also being used to investigate the genetic and epigenetic biomarkers of antibiotic resistance and the effects of different oral antibiotic combinations on bacterial genomes and the gut microbiome.

Combining oral antibiotics prevented the spread of antibiotic resistant genes. Low dose monotherapy treatment increased antibiotic resistant genes but did not greatly change bacteria diversity.

DRUG-DRUG INTERACTIONS

As patients often use more than one drug at a time, it is critical to know if drugs taken together interact, which can lead to safety or efficacy implications. To collect this information, FDA may require drug-drug interaction (DDI) studies. DARS evaluated the best methods to use for DDI studies for the following cases:

- **P-glycoprotein (P-gp) efflux transporter:** DARS is examining whether differences in the use of different cell lines and IC50 calculation methods to assess P-gp inhibition influence the prediction of potential clinical DDIs.
- **Sunscreen DDI:** DARS is using transfected cells to evaluate whether absorbed sunscreen active ingredients inhibit uptake transporters in the liver and kidneys which may lead to clinical DDIs.
- **Uridine diphosphate glucuronosyltransferases (UGTs):** DARS is reviewing the scientific literature to compile data for recommendations on standardizing in vitro UGT-based DDI studies.

Relevant publications

Volpe et al. Xenobiotica 2022, 1-7.

Mahamoud et al. J Clin Psychopharmacol 2022, 42(3):238-46.

Raplee et al. Antimicrob Resist Infect Control 2021, 10:36.

Garimella et al. Int J Antimicrob Agents 2020, 55:105861.

Microphysiological Systems and Induced Pluripotent

LIVER MICROPHYSIOLOGICAL SYSTEM (MPS)

Liver microphysiological systems (MPS, also known as organ-on a-chip) were introduced over 10 years ago as promising tools for predicting drug-induced liver injury of drugs. However, they are still not routinely used in regulatory applications, in part due to a lack of criteria for ensuring reproducibility of results. Experimental work performed by DARS indicate that a well characterized liver MPS can produce reliable and reproducible toxicity, metabolism, and drug distribution results that are generally in agreement with clinical data. MPS offers drug developers a new approach to test new therapies for patients with unmet medical needs. An additional advantage of MPS is that cells derived from a human organ may be used, making the predictions derived from the system more relevant to patients. Furthermore, MPS helps to promote the principles of the 3Rs (replacement, reduction and refinement) of animal experimentation in the drug development process.

Relevant publications

Baran et al. ALTEX 2022, 39(2).

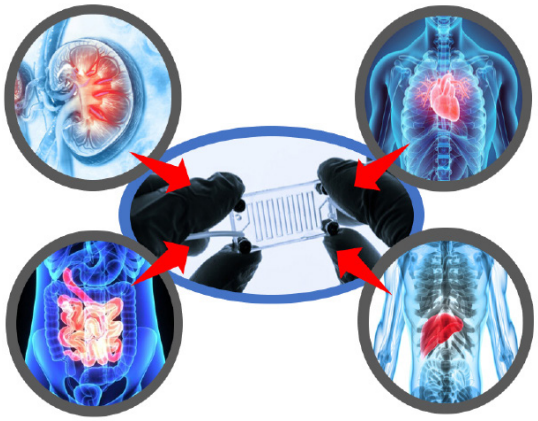
Yang et al. Toxicol Sci 2022, 190(2):117-126.

Rubiano et al. Clin Transl Sci 2021, 14:1049-61.

Qosa et al. J Pharmacol Toxicol Methods 2021, 110:107083.

HUMAN INDUCED PLURIPOTENT STEM CELLS

Human Induced Pluripotent Stem Cells (iPSCs) are cells created in the lab and can be any cell type found in the body, including heart and liver. The goal is to use iPSC-engineered heart cells to predict adverse cardiac effects caused by a drug as well as a drug's effect on the heart of an individual patient based on their genes. DARS is also studying iPSC engineered liver cells, in particular how well iPSC-derived liver cells predict drug-induced liver injuries in patients.



Safety Pharmacology and Toxicology

ANALYSIS OF SECONDARY PHARMACOLOGY ASSAYS

Secondary pharmacology assays are cell-based studies that can identify potential safety issues before entering human clinical trials. However, there is little guidance on which targets should be studied and how the study results should be communicated to FDA. DARS evaluated 1120 studies submitted by pharmaceutical companies and created a database for reviewers. Results from this study will inform the best methods for communicating study results and evaluate the need for a standardized list of drug targets for testing. To assist with this effort, DARS recently entered into a Public-Private Partnership with the Pistoia Alliance, a not-for-profit alliance of life science organizations that work together to lower barriers to innovation in research and development.

Relevant publications

Scott et al. J Pharmacol Toxicol Methods 2022, 117:107205.

Dodson et al. J Pharmacol Toxicol Methods 2021, 111:107098.

Ren et al. PLoS One 2022, 17(11):e0276995.

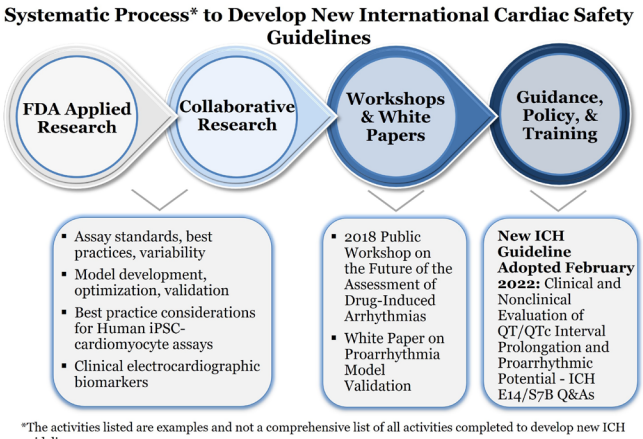
King et al. J Pharmacol Toxicol Methods 2022, 118:107229.

IMMUNE MEDIATED ADVERSE EVENTS

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. This can occur with some of the most promising new cancer treatments. DARS is comparing the ability of different nonclinical models to predict immune-mediated adverse effects of biological products.

MODERNIZING CARDIAC SAFETY EVALUATION

It is critical to harmonize drug development requirements among drug regulators globally. New guidelines from the ICH for assessing the cardiac safety of all new drugs were adopted in 2005. While these guidelines were successful in many ways, concerns that nonclinical data were not being leveraged in clinical decision making were identified. DARS has previously led numerous studies that informed the development of a new integrated nonclinical-clinical guidelines. DARS' current research effort continues to provide insights regarding the extent of experimental uncertainties in nonclinical data and methods to account for these uncertainties in risk prediction processes. These studies include a multi-site cardiac ion channel effort that seeks to establish intra- and interlaboratory data variability on 30 clinical drugs and a new dataset for in silico ventricular myocyte development.



Computational Pharmacology and Toxicology

(Q)SAR MODEL DEVELOPMENT

DARS is developing computational models, known as (Quantitative) Structure Activity Relationship models [(Q)SAR], that can be used to assess a compound's toxicological and pharmacological properties in absence of empirical data. Models being developed include:

- **Blood brain barrier:** Predicts the potential for a drug to cross the blood-brain barrier. A manuscript was recently published in Frontiers in Pharmacology.
- **Cardiotoxicity:** Models have been developed to predict cardiotoxicity to assist with drug safety assessment.
- **Cytochrome P450:** DARS is developing (Q)SAR models to help identify mechanism-based structural alerts in a metabolite for CYP inhibition studies.

Relevant publications

Bai et al. J Pharm Sci 2022, S0022-3549(22):00472-5.

Bai et al. Methods Mol Biol 2022, 2486:87-104.

Faramarzi et al. Front Pharmacol 2022, 13:1040838.

EVALUATING NITROSAMINE SAFETY

DARS collaborated on the development of a computational method to identify surrogates for nitrosamine drug impurities using chemical structure. This facilitates the evaluation of these impurities for carcinogenic potency and can inform setting regulatory limits for a drug product.

QUANTITATIVE SYSTEMS PHARMACOLOGY (QSP) MODELING

QSP is a computational approach for modeling and simulating drug responses, which mechanistically links drug target(s) of a proposed drug product through its pharmacological network to drug responses. DARS is evaluating potential roles for QSP modeling to inform regulatory decision making. Additionally, a database of QSP submissions is regularly updated to better understand current QSP modeling practices and identify opportunities for QSP in drug development.

Generic Drugs and Biosimilars Overview

DARS performs studies to advance the use of new drug development tools for streamlining the development of complex generics and biosimilar products.

Selected Generic and Biosimilars Product Activities

IMMUNOGENICITY OF COMPLEX GENERICS AND BIOSIMILAR PRODUCTS

IImpurities associated with the synthesis of generic peptide drugs raise concerns about immunogenicity from these products. DARS is assessing methods to predict immunogenicity of peptide impurities using different types of nonclinical models. These methods can also be applied to other product categories, including biosimilar products.

INJECTABLE DELAYED-RELEASE GENERIC DRUGS

DARS is studying the ability of a computational model to design bioequivalent (and non-bioequivalent) injectable delayed-release generic drug products based on a reference listed drug. This research will help FDA guide industry on the data requirements for approval of model-designed complex generic drugs.

Efficient Biosimilar Product Development and Approval

ADVANCING THE USE OF BIOMARKERS TO STREAMLINE BIOSIMILAR PRODUCT DEVELOPMENT

A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from a previously FDA-approved biological product. To ensure patients realize the benefit of a robust, competitive market for biosimilar products, DARS is focused on improving the efficiency of biosimilar product development and approvals by advancing the use of pharmacodynamic (PD) biomarkers. This includes:

- Developing an evidentiary framework to advance the use of PD biomarkers for biosimilar products.
- Conducting three clinical studies to define best practices on characterizing PD biomarkers for different classes of biological products and to develop general considerations applicable to all types of biomarkers for biological products.
- Evaluate uses of proteomic and transcriptomic analysis of human plasma to identify novel biomarkers for biosimilar product development.
- Holding a joint FDA/Duke Margolis Workshop to discuss initial findings and facilitate a broader discussion on the use of PD biomarkers for biosimilar product development.
- Manuscripts for each of the above topics will be included in the January 2023 themed issue on Innovations in Biosimilars in the journal Clinical Pharmacology & Therapeutics.

Relevant publications

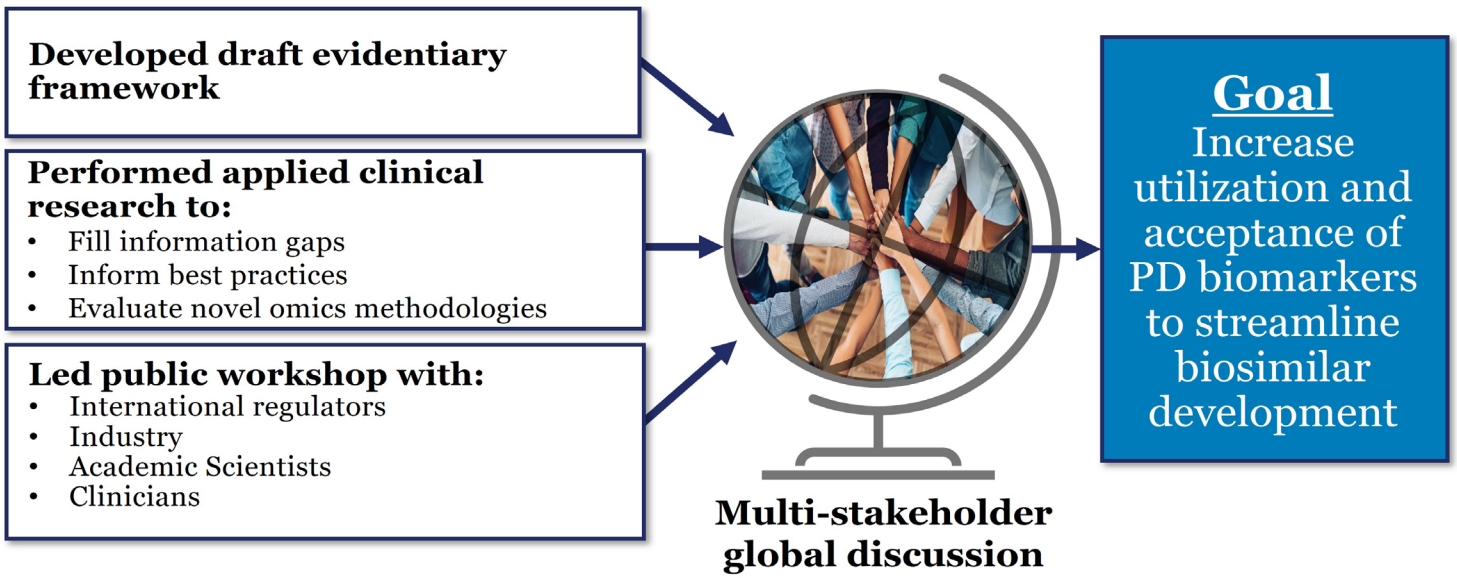
Gershuny et al. Clin Pharmacol Ther 2022.

Hyland et al. Clin Pharmacol Ther 2022.

Florian et al. Clin Pharmacol Ther 2022.

Sheikhy et al. Clin Pharmacol Ther 2022.

Florian et al. Clin Pharmacol Ther 2022.



Policy, Guidance, and Review Highlights

DARS leads or participates in multiple review teams, working groups, and task forces. This has included teams focusing on COVID-19 safety issues, drug approvals, and vaping-associated lung injury.

Selected Policy and Guidance Activities

POPULATION PHARMACOKINETICS: FINAL GUIDANCE

Population pharmacokinetic (PopPK) analysis is a well-established, quantitative method that can explain some of the variability in drug concentrations among individuals by integrating all relevant pharmacokinetic information across a range of doses and populations to identify factors that can affect a drug's exposure. The focus of this guidance is on the use of this approach in explaining the variability in drug concentrations observed among human trial subjects from intrinsic factors, extrinsic factors, differences in dosing, and routes of administration. This guidance includes common applications of PopPK analysis to inform drug development and FDA's current thinking on data and model submissions to support regulatory decisions, recommendations on how to incorporate information from PopPK analyses in labeling, and the general expectations regarding the format and content for PopPK reports submitted to the Agency.

E14 AND S7B CLINICAL AND NONCLINICAL EVALUATION OF QT/QTC INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL - QUESTIONS AND ANSWERS, GUIDANCE FOR INDUSTRY

While the 2005 ICH guidelines for assessing cardiac safety for all new drugs were successful in many ways, there were concerns that nonclinical data was not being leveraged to inform clinical decision making. To address limitations, DARS has led numerous studies both at FDA and through coordinating multi-site studies with public-private consortia. Based on the new science, DARS led the ICH working group on revising the guidelines, and in 2022, FDA issued a question and answer guidance to clarify key issues to facilitate implementing the ICH guidelines E14 and S7B.

Regulatory Consults and Numbers

DARS performs expert regulatory consultations and reviews on critical regulatory and public health needs to address out of the ordinary questions that the primary review division may be unsure how to approach or has not seen before.

DARS assemble diverse, multidisciplinary teams to approach a problem from multiple angles and think outside the box.

Questions from these consults often become the foundation for applied research studies to fill regulatory knowledge gaps, enhance drug development, and facilitate review.

CONSULTS COMPLETED

- Office of New Drugs
- Office of Surveillance and Epidemiology
- Office of Translational Sciences
- Safety and mechanism of action
- Labeling
- Protocol review
- Bioanalytical analysis

18

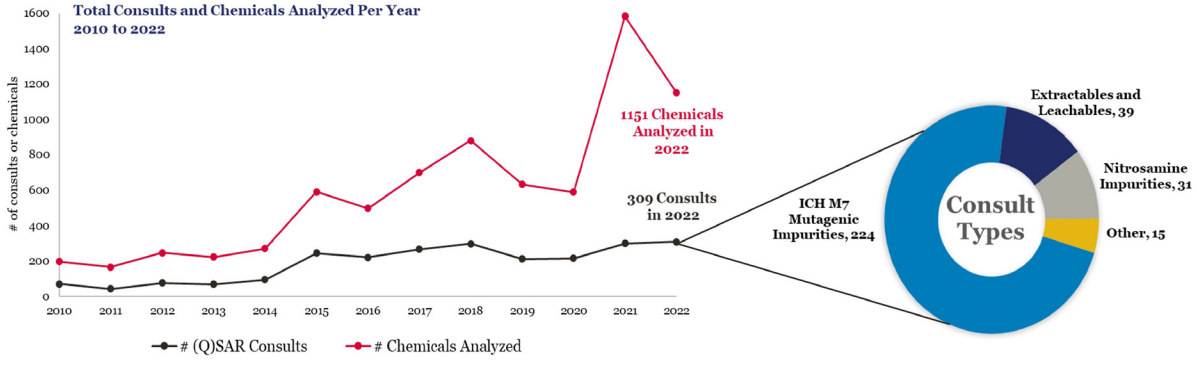
Regulatory consults and review team activities completed in 2022

(Q)SAR Consults

In addition to the consults covered above, the DARS Computational Toxicology Consultation Service (CTCS) performs consultation-based reviews of (Quantitative) Structure-Activity Relationship [(Q)SAR] analyses submitted by pharmaceutical companies for drug impurities—including nitrosamines—and extractable/leachable compounds from container closure and drug delivery systems. When needed, CTCS generates (Q)SAR predictions and performs cheminformatic analyses in-house to fill data gaps. CTCS provides (Q)SAR consultations supporting pre- and post-market regulatory decision-making for new and generic drug products for 20 chemical structures on average per week.

309

Consults completed in 2022



Contact Us

DARS closes the gap between scientific innovation and regulatory review.

DARS staff at a team event in the Fall of 2022.

The Division of Applied Regulatory Science (DARS) closes the gap between scientific innovation and regulatory review by moving new science into the CDER review process. Through rapidly formed interdisciplinary teams, DARS tackles challenging scientific questions and conducts mission-critical research that impact the development and regulatory review

Want to learn more about DARS?

DARS Website

Contact: DARS@fda.hhs.gov

U.S. FOOD & DRUG
ADMINISTRATION

U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
www.fda.gov