U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Clinical Pharmacology
Division of Applied Regulatory Science

2025 Annual Report

Contents

Message from the Acting Director

The Division of Applied Regulatory Science (DARS) had another strong year delivering applied regulatory science research in ongoing collaborations with stakeholders across FDA to enhance regulatory decision making and address emerging public health issues.

With the Center for Tobacco Products (CTP), DARS is defining differences in physiological effects between natural and synthetic nicotine to help inform CTP's regulatory approach. With Office of New Drugs (OND) and Center Director staff, DARS continues to use modeling to inform drug development and best practices for addressing opioid misuse and conducted a clinical study to evaluate liver toxicity risk associated with unregulated cannabidiol product use.

Other DARS and OND collaborations are advancing regulatory applications of new approach methodologies (NAMs) and developing drug review tools to enhance reviewer efficiency. DARS initiated collaborations with the Office of Women's Health to investigate the impact of menopause on drug metabolism and the Perinatal Health Center of Excellence to study drug movement across the blood-milk barrier in lactating women.

Rodney Rouse
DVM, PhD, MBA
Acting Director, Division of Applied Regulatory Science

The rest of this report provides a larger sampling of the many 2025 efforts of DARS dedicated staff that I hope you will review. These accomplishments reflect the dedication to mission of a highly collaborative and expert staff who motivate me to be a stronger leader and advocate for them. Congratulations DARS on another great year! You have set a foundation for an even better 2026.

49 Applied Research Projects in 2025

15 Global Collaborations

3 Broad Agency Agreements

6 Research Collaboration Agreements

2 Material Transfer Agreements

4 Centers Of Excellence in Regulatory Science and Innovation (CERSI)

20
External Presentations Delivered

19
External Posters Presented

30 Manuscripts Published

Completed Projects

Cannabidiol and Liver Enzyme Level Elevations in Healthy Adults

Despite growing use, limited safety data exists on consumer use of unregulated cannabidiol (CBD) products. DARS conducted a rigorous clinical trial to study CBD's effects in healthy participants and to identify associated molecular markers at doses typical of consumer use (350 mg/day). Additionally in support of the study, DARS developed and validated a rapid high-throughput bioanalytical method for the quantification of cannabidiol and its primary metabolites in human plasma.

Elevated liver enzymes and increased eosinophilia in those exposed to CBD doses lower than the prescription drug product dosage were observed; however, no differences were observed between CBD and placebo groups on endocrine hormones. A significant pharmacokinetic interaction between CBD and citalopram was observed, suggesting the potential for drug interactions leading to unintended increased drug exposure, while interactions between CBD and morphine were limited. Preliminary findings also highlighted potential associations with inflammation and liver dysregulation.

This trial not only provides safety information on unregulated CBD consumer products but also highlights the need for further investigation on effects of long-term use of these products.

Read More

- **JAMA Internal Medicine:** Cannabidiol and Liver Enzyme Level Elevations in Healthy Adults
- Regulatory Science in Action

Opioids, Drug Interactions and Respiratory Depression

DARS conducted a series of clinical trials studying if the interaction between opioids and psychoactive drugs affect respiratory depression. One study showed that while midazolam co-administered with oxycodone did not decrease hypercapnic ventilation compared with oxycodone alone, the combination significantly affected other ventilatory measures. A subsequent part of this study found that paroxetine combined with oxycodone decreased ventilation compared to oxycodone alone.

In a study with longer periods of dosing, results showed that both paroxetine and escitalopram, alone and co-administered with oxycodone, decreased hypercapnic ventilation by day 7 of administration and this persisted for the study's dosing duration (21 days). These results build upon previous study findings and suggest that selective serotonin reuptake inhibitors (SSRIs) may have a class effect on hypercapnic ventilation that persists with chronic use.

Read More

- **British Journal of Anaesthesia:** Effect of Midazolam Co-Administered with Oxycodone on Ventilation: a Randomised Clinical Trial in Healthy Volunteers

Completed Projects

Advancing New Approach Methodologies (NAMs) in Drug Development

DARS, in collaboration with the Office of New Drugs, applied research on human cardiac NAMs to reduce animal testing dependence. Through rigorous characterization and protocol development, DARS scientists demonstrated that these models successfully replicate clinical outcomes, accurately detecting heart safety issues. This research also establishes comprehensive best practices and context-of-use recommendations to help accelerate drug development while enhancing regulatory review processes through more predictive, human-relevant safety assessments.

Read More

- **Nature Portfolio:** Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes and Their Use in a Cardiac Organ-on-a-Chip to Assay Electrophysiology, Calcium and Contractility
- **Journal of Cardiovascular Development and Disease:** Nonclinical Human Cardiac New Approach Methodologies (NAMs) Predict Vanoxerine-Induced Proarrhythmic Potential

Establishment of a Lung New Approach Methodology (NAM) for Drug Permeability Assessment

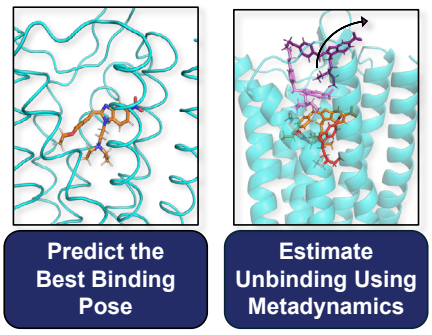
In collaboration with the Office of Generic Drugs, DARS is studying a lung NAM that offers increased precision in measuring inhaled drug permeability. Successfully characterized using bronchodilators for COPD and asthma treatment, this innovative model provides regulators with more accurate permeability assessments for informed decision-making potentially accelerating therapeutic development while enhancing patient safety.

Read More

- **ACS Pharmacology & Translational Science:** A 3D Model of the Human Lung Airway for Evaluating Permeability of Inhaled Drugs
- **Frontiers in Pharmacology:** Assessment of Drug Permeability Using a Small Airway Microphysiological System

Nitazenes

Nitazenes are synthetic opioids with a 40-fold greater potency than fentanyl and have been linked to an increase in overdose mortality. DARS, in collaboration with the U.S. Department of Veterans Affairs and University of Maryland, developed a sophisticated computer modeling method to predict the unbinding kinetics of nitazenes from the opioid receptor. This method can be used to evaluate overdose risk potential as opioids and other emerging substances of misuse with prolonged receptor dissociation kinetics are more difficult to treat.



Read More

- **Neuropharmacology:** A Putative Binding Model of Nitazene Derivatives at the μ-Opioid Receptor

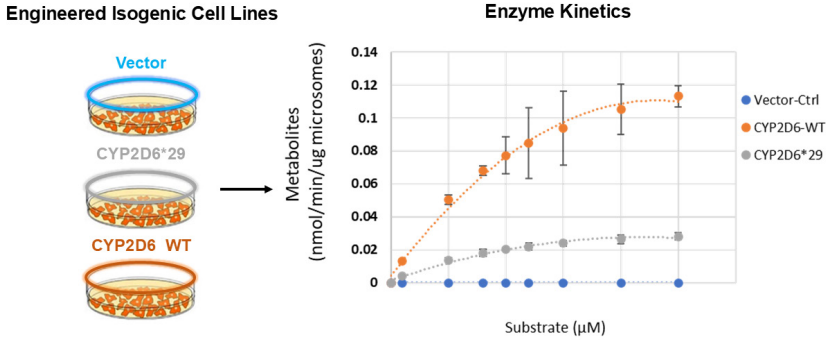
Updates to Ongoing Projects

R-Nicotine in Tobacco Products

Nicotine exists in two enantiomeric forms: S-nicotine and R-nicotine. S-nicotine predominates in tobacco-derived nicotine (TDN) products; however, the growing use of non-tobacco nicotine (NTN) has introduced the R-enantiomer to the marketplace. As limited data regarding the effects of R-enantiomer exists, DARS and the Center of Tobacco Products are studying both forms using new approach methodologies (NAMs). Study results will determine if using NTN affects the body differently compared to TDN and whether R-nicotine could pose different public health risks than S-nicotine. Ultimately, results will contribute to science-based decision-making regarding tobacco products containing R-nicotine and help inform FDA's regulatory approach.

Validating In Vitro Cell-Based Models for Characterizing Rare Drug Metabolizing Variants

To understand the impact of rare genetic variants of metabolizing enzymes, DARS, in collaboration with the Division of Translational and Precision Medicine, engineered HEK293 cell models to compare the metabolism of a well known clinically meaningful enzyme variant of a gene compared to the common version of the same gene. Preliminary studies demonstrated that the variant enzyme CYP2D6*29 exhibited significantly reduced drug metabolizing activity compared to its common version, concordant with clinical data. Demonstrating that these cell models are able to reflect activity thresholds of clinical significance will allow future researchers to utilize these models with higher confidence to predict the impact on metabolism of understudied gene variants, including understanding genetic variants of unknown clinical significance.



Quantitative Benefit-Risk Assessment for Overdose Reversal and Withdrawal

Over the past 5 years, DARS has developed translational models to quantitatively translate benefits found for surrogate endpoints in clinical studies into more meaningful real-world endpoints. DARS is expanding an existing systems pharmacology model to cover important risk endpoints, including both common and rare withdrawal symptoms. Combined with previous work, this will be used to establish a quantitative framework to characterize benefit-risk assessment for opioid reversal agents.

Read More

- **Clinical Pharmacology & Therapeutics:** Toward Developing Alternative Opioid Antagonists for Treating Community Overdose: A Model-Based Evaluation of Important Pharmacological Attributes

New Projects

Evaluating The Effects of Oral Delta-9-Tetrahydrocannabinol (Δ9-THC) With and Without Alcohol on Perception and Driving Performance

With the rise of intoxicating cannabis product use, it is critical to understand how low-dose (5-10 mg) oral Δ9-THC in recreational users affects self-perception of driving impairment as well as actual driving performance, both alone and when combined with alcohol. DARS and the Controlled Substance Program are studying these effects in recreational users and will also compare outcomes to an established alcohol-related impairment benchmark of blood alcohol content (0.08% BAC). Findings will clarify links between Δ9-THC dose, subjective effects, and driving performance, supporting evidence-based guidance on cannabis recreational use and driving safety.

Influence of Menopause on Drug Metabolism and Transport

The effects of menopause and changing sex hormone levels on the pharmacokinetics (metabolism, distribution, elimination) of drugs has not been well researched. Through research in collaboration with FDA's Office of Women's Health, DARS will examine the effects of sex hormones, mimicking pre- and post-menopausal levels, on in vitro drug metabolism and transport. Results from this study may also inform the design of clinical trials comparing the pharmacokinetics of selected drugs in pre- versus post-menopausal women.

Cardiac New Approach Methodologies (NAMs) Assessment of Drug Combinations

Given that patients often use more than one drug at a time, it is critical to know whether drugs taken together interact to positively or negatively impact safety or efficacy. DARS used a novel cardiac NAM to study the combination of cobicistat and moxifloxacin, finding that cobicistat reduced the cardiac repolarization prolongation risk induced by moxifloxacin. While this study demonstrated protective effects as a result of the interaction, the same assay can also identify combinations that exacerbate cardiac problems. This work provides a model for in vitro evaluation of drug combinations to inform regulatory decision-making.

Read More

- **Frontiers in Drug Discovery:** Towards Human Cardiac New Approach Methodologies (NAMs) to Evaluate the Combination of Repolarization Prolonging and Shortening Drugs: A Pilot Study

New Projects

Neural New Approach Methodologies (NAMs)

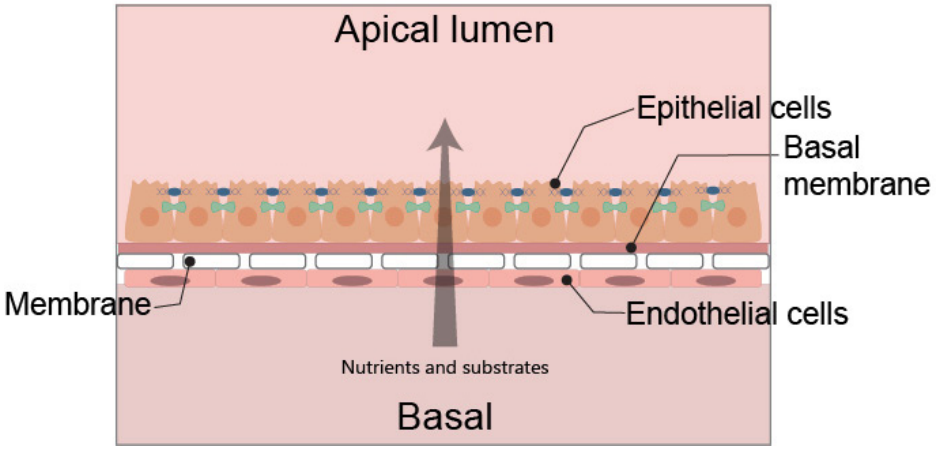
Aligned with FDA's 2025 Roadmap to Reducing Animal Testing in Preclinical Safety Studies, DARS is leading research using a human neural NAM to directly address critical opioid challenges including over-utilization, opioid use disorder, and synthetic opioids, and to expand treatment and reversal options. This cutting-edge research facilitates NAM adoption into the regulatory review processes and is one example of DARS's commitment to advancing complex in vitro models.

Read More

- **NAM Journal:** Nonclinical Human Neural New Approach Methodologies (NAMs): Electrophysiological Assessment of Opioid Agonist and Antagonist Combination

Applying a Microphysiological System to Predict Drug Transfer Across the Blood-Milk Barrier

A new DARS study supported by the Perinatal Health Center is developing a microphysiological system (MPS) model of the human blood–milk barrier to better understand how medications transfer into breast milk. Existing tools offer limited predictive power, leaving a significant gap in data to guide safe medication use during lactation. This novel MPS model recreates key features of the lactating mammary epithelium. Once established, it will be used to evaluate the permeability of commonly prescribed medications, providing a more accurate and ethical platform to support maternal treatment decisions during breastfeeding.



Microphysiological System

Review and Guidance

Enhancing Cardiac Safety Review: CiPA-Driven Tools for Regulatory Review

Human induced pluripotent stem cell-derived cardiomyocyte (hiPSC-CM) data were only recently incorporated with safety pharmacology submissions, enabling a more thorough cardiac risk assessment. To enhance reviewer efficiency and streamline processes, DARS and the Office of New Drugs are developing essential reviewer tools to predict clinical proarrhythmic risk. This integrated approach advances cardiac safety assessment by combining human-relevant models with practical regulatory tools for improved decision-making.

Carcinogenic Potency Categorization Approach (CPCA) Calculator Tool

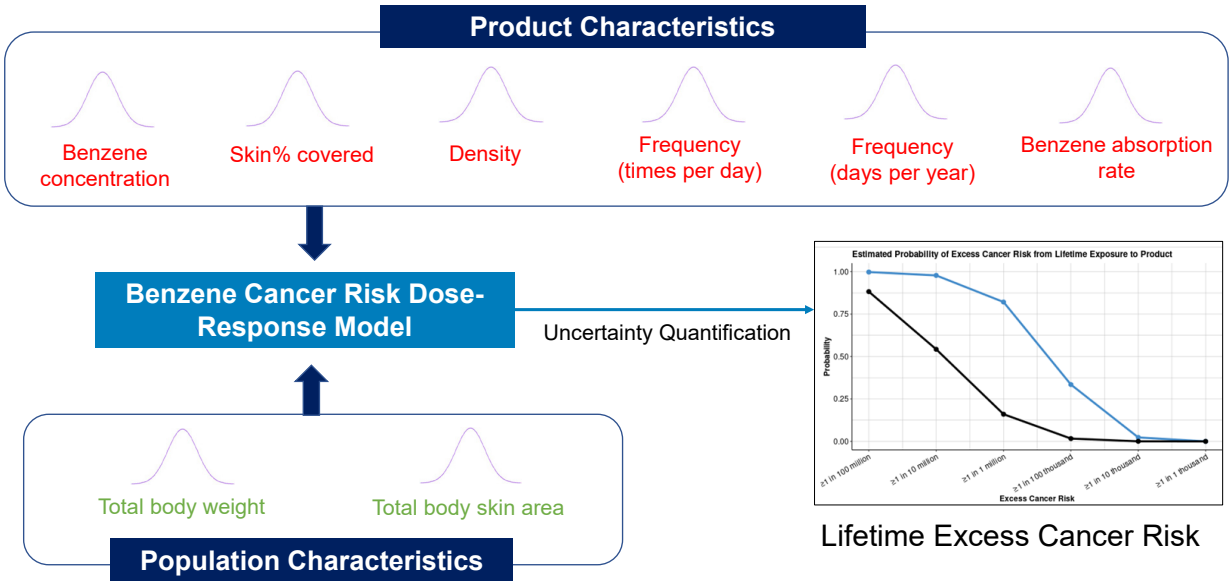
The Carcinogenic Potency Categorization Approach (CPCA) uses an applied structure-activity relationship model to determine an acceptable intake (AI) limit for nitrosamine impurities when empirical data are unavailable. In 2025, DARS implemented a CPCA calculator for reviewers to independently confirm CPCA-based AI calculations submitted by industry, thereby increasing review efficiency.

Read More

- **Regulatory Toxicology and Pharmacology:** Determining Recommended Acceptable Intake Limits for N-nitrosamine Impurities in Pharmaceuticals: Development and Application of the Carcinogenic Potency Categorization Approach (CPCA)
- **CDER Spotlight:** Determining Recommended Acceptable Intake Limits for N-nitrosamine Impurities in Pharmaceuticals: Development and Application of the Carcinogenic Potency Categorization Approach

Risk Assessment Visualization Tool

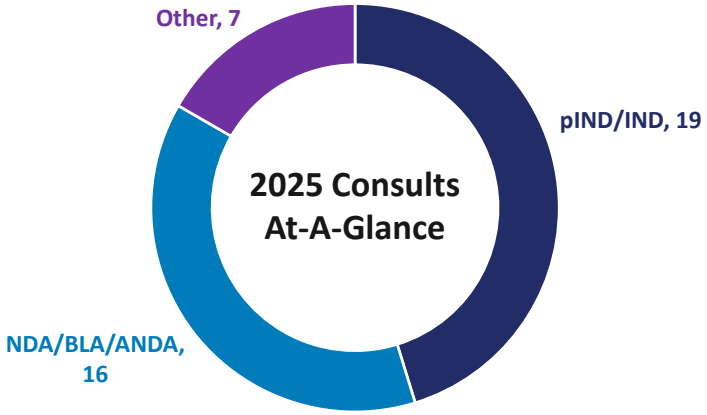
DARS continued the development of a quantitative and user-friendly tool for conducting risk assessment of impurities and contaminants, such as benzene (a known carcinogen). This tool has been used to support recall classification decisions regarding alleged benzene contamination in some common topical drug products.



Lifetime Excess Cancer Risk

Regulatory Consultations

DARS performs expert regulatory consultations and reviews to address questions related to mechanism of action, appropriateness of methodological approaches and interpretation of regulatory findings from FDA reviewers and scientists. Two example consults are below:



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Consults completed in 2025

Consult Highlight: Monitoring Natural and Synthetic Kratom Analogs

A multi-component analysis was performed to evaluate identified kratom alkaloids and their synthetic analogs, combining structural analysis, pharmacological assessment, and molecular modeling to understand their binding at μ-opioid receptor. A database for 100 naturally occurring kratom alkaloids and synthetic analogs was developed that included structural and pharmacological data, when available. Findings from this assessment show that there are multiple highly potent analogs, highlighting the need for continued monitoring.

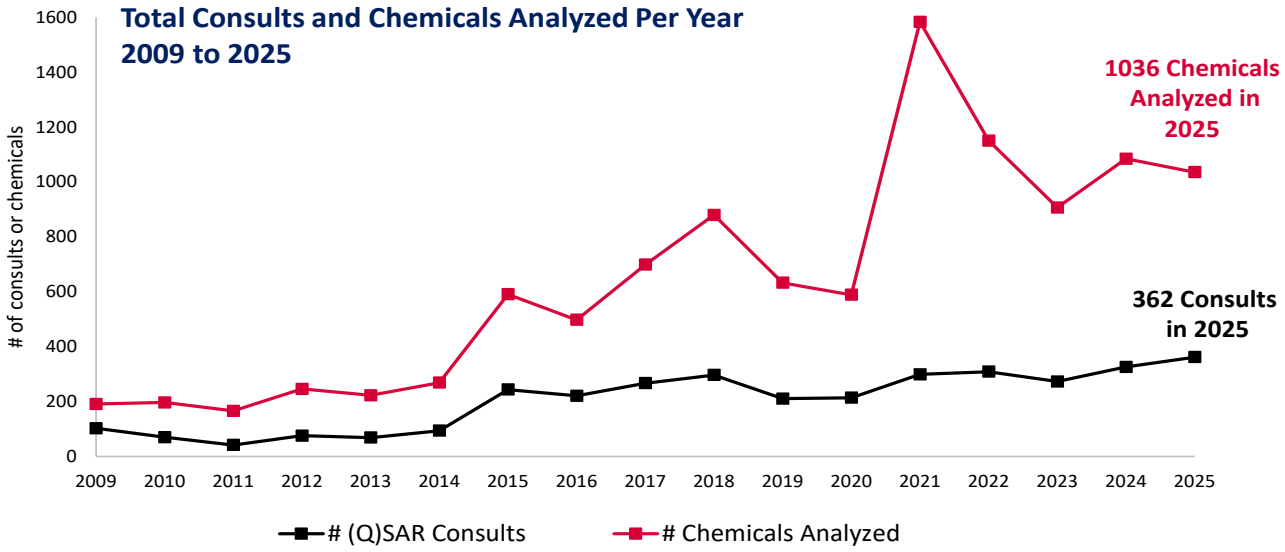
Consult Highlight: Postmarketing Safety Surveillance for Cystic Fibrosis Treatment

Trikafta (elexacaftor/tezacaftor/ivacaftor) tablets and granules are a CFTR modulator approved for treating cystic fibrosis in patients aged 2 years and older who have at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on clinical and/or in vitro data. Since approval, cases of intracranial hypertension have been reported in the post-marketing setting. DARS identified two plausible pathogenic mechanisms: altered CSF equilibrium secondary to drug effects on the choroid plexus and hypervitaminosis A. Following DARS' assessment, FDA required the drug manufacturer of this product and other CFTR modulators to make safety labeling changes adding a Warning and Precaution regarding the risk of intracranial hypertension.

Drug Development Tools

ISTAND's goal is to support the development of novel approaches to drug development that may be acceptable for regulatory use. In 2025, DARS contributed to the review of **11** unique Drug Development Tool (DDT) submissions.

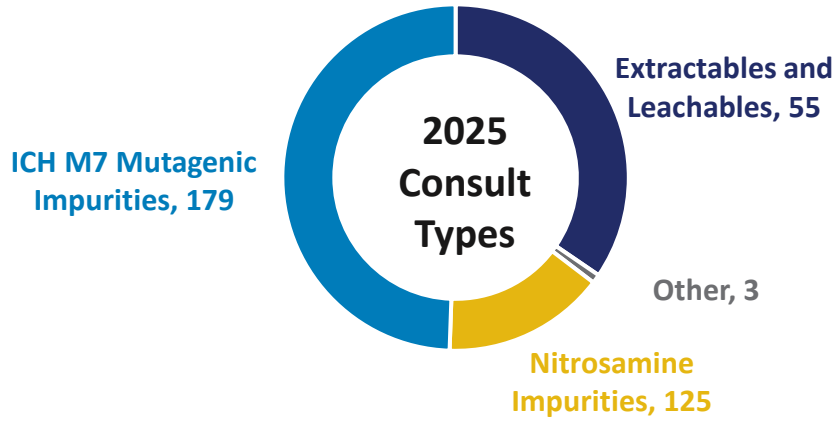
Regulatory Consultations: (Q)SAR Consults



362

Consults completed in 2025

The DARS Computational Toxicology Consultation Service performs consultation-based reviews for FDA 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, DARS generates (Q)SAR predictions and performs cheminformatic analyses in-house to inform review of submissions. DARS provides (Q)SAR consultations supporting pre- and post-market regulatory decision-making for new and generic drug products for an average of 89 chemical structures per week.



Learn More

DARS Overview

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