U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF CLINICAL PHARMACOLOGY

DIVISION OF APPLIED REGULATORY SCIENCE

2023 Annual Report

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www.fda.gov

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Director's Message

2023 marked the 10-year anniversary of the Division of Applied Regulatory Science (DARS). Over the past decade, DARS has grown significantly as it advanced its vision to move new science into the FDA regulatory process and address emergent regulatory and public health questions.

DARS' accomplishments have included conducting landmark applied research studies that were not being conducted by other stakeholders, such as whether sunscreen active ingredients are absorbed into the blood stream. Other work has involved performing high-quality research to seek the truth about critical public health questions, such as whether common over-the-counter medications convert to carcinogens, and effectively communicate the findings to fight misinformation. Furthermore, DARS has leveraged its scientific credibility and regulatory knowledge to lead the development of new policy and guidance documents both at FDA and through international harmonization efforts.

In the past year DARS embarked on implementing a 3-year strategic plan and roadmap that seeks to set standards for high quality applied research and build a sustainable infrastructure to support quality. Initiatives to meet these goals including evaluating key components of successful projects, implementing industry-proven processes, mentoring future leaders, and opening new communications channels.

I am excited to see how DARS staff expand their impact in 2024 by engaging stakeholders in mission-critical laboratory, computational, and clinical applied research to inform regulatory decision-making and to address public health. Thank you to all the DARS staff and our collaborators within and outside of FDA

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

Organization

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. Staffed by experts across the translational research spectrum, DARS forms synergies by pulling together scientists and experts from diverse backgrounds to collaborate in tackling some of the most complex challenges facing FDA.

OUR MISSION

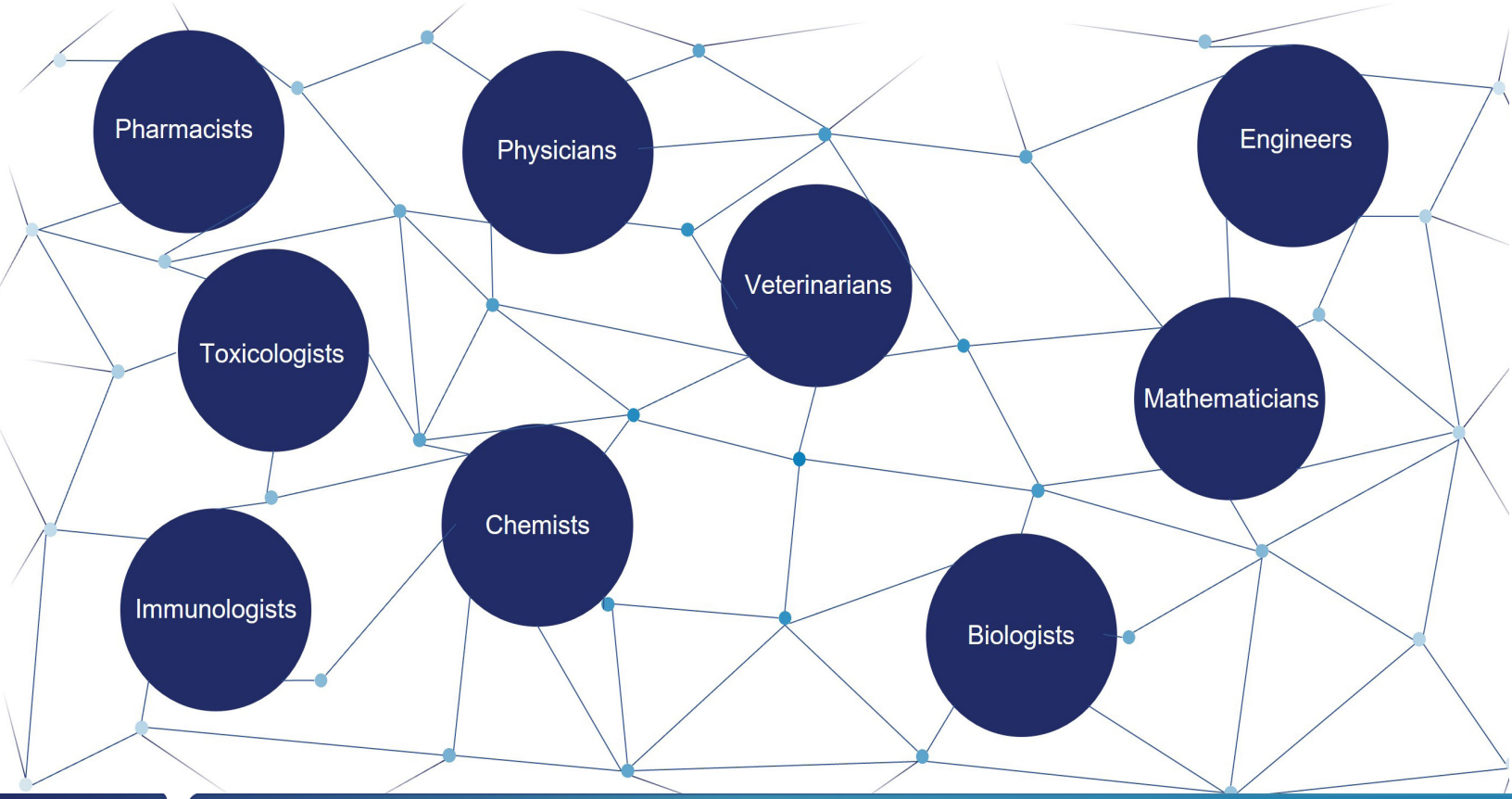
To engage stakeholders in mission-critical laboratory, computational, and clinical applied research to inform regulatory decision-making and to address public health.

OUR VISION

To move new science into the FDA regulatory process and address emergent regulatory and public health questions.

> *Translation*, in its most holistic sense, bridges scientific, operational, and cultural gaps to advance scientific knowledge for the benefit of patients and the greater public. Over the last decade, our exceptional scientists and staff in DARS have shown they are not only up for the challenge, they are at the forefront of solutions.

Dr. Issam Zineh
Office of Clinical Pharmacology Director



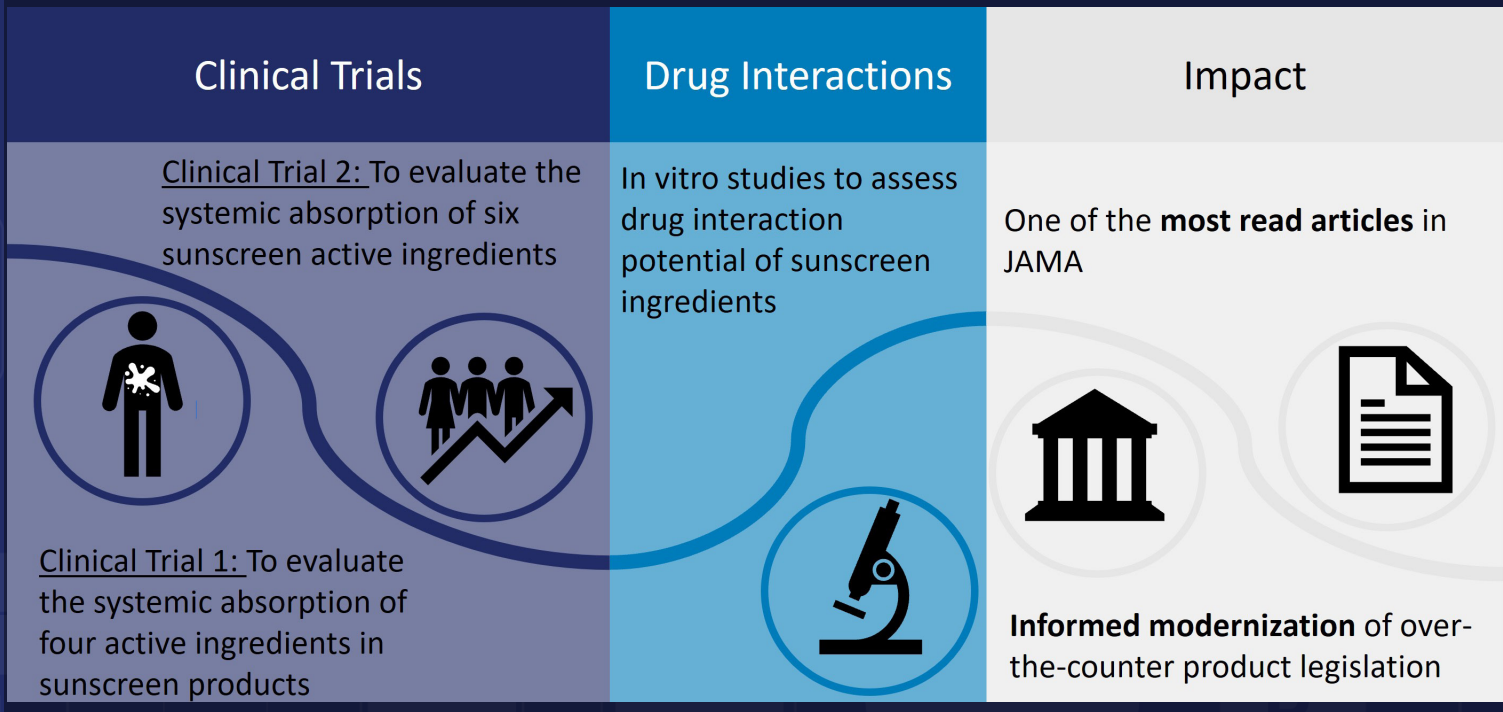
10 Years of DARS

Shedding Light on Sunscreen: The Impact of Research on New Legislation

Sunscreens are a widely used over-the-counter product, but there are gaps in the existing data about the absorption and safety of some sunscreen active ingredients. A proposed rule requested additional safety data for 12 sunscreen active ingredients to help address these gaps. To show the feasibility of the requested studies and provide more evidence about the absorption of some sunscreen ingredients, DARS conducted two clinical trials to assess the systemic exposure of sunscreen ingredients. These studies demonstrated that maximum usage sunscreen clinical trials are feasible, that some sunscreen active ingredients are absorbed at levels that would trigger additional safety studies, and that further research is needed to fill in data gaps for sunscreen ingredients. DARS' studies were cited in a proposed order on sunscreens.

DARS additionally conducted in vitro studies to assess the potential for drug-drug interactions and identify the metabolites of sunscreen active ingredients.

The results of these studies helped FDA better understand sunscreen ingredient absorption and informed the modernization of sunscreen and other over-the-counter product legislation.



NOTABLE REFERENCES

DARS Publications

Proposed Order: Amending Over-the-Counter Monograph M020: Sunscreen Drug Products for OTC Human Use

Proposed Rule: Sunscreen Drug Products for Over-the-Counter Human Use

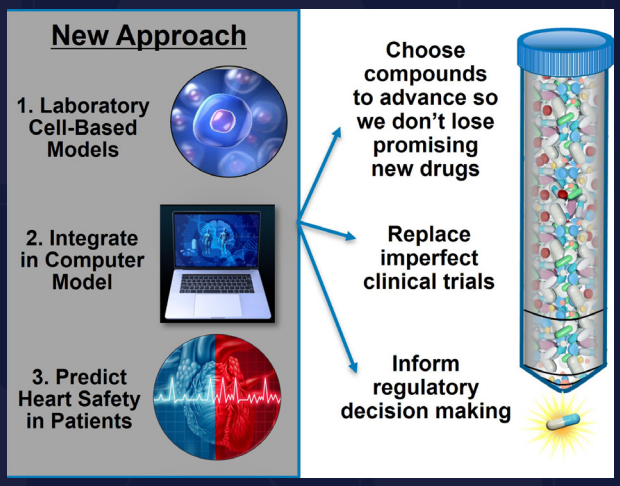
Implementing Regulatory Science: Updating International Regulatory Guidelines in Cardiac Safety

In 2005, ICH guidelines for assessing the cardiac safety of all new drugs were adopted by drug regulators around the world. While they were successful in many ways, they also had limitations, including that nonclinical data was not being leveraged to inform clinical decision making.

In response, the Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative was implemented by FDA in collaboration with industry, academics, and other global regulators to improve the assessment of drug-induced cardiac toxicity. Through CiPA, DARS led studies to assess:

- in vitro ion channel assay standards, best practices, and variability
- in silico computational model development, optimization, and validation
- best practice considerations for human iPSC cardiomyocyte assays
- clinical electrocardiographic biomarkers

DARS staff served as lead in developing Questions and Answers for ICH E14/S7B as a new guideline. This guideline contains best practice recommendations for in vitro ion channel and human induced pluripotent stem cell assays to enable use as follow up studies in place of potential animal studies and principles for validating in vitro and in silico proarrhythmia models and qualifying them for regulatory use, which can reduce animal use.



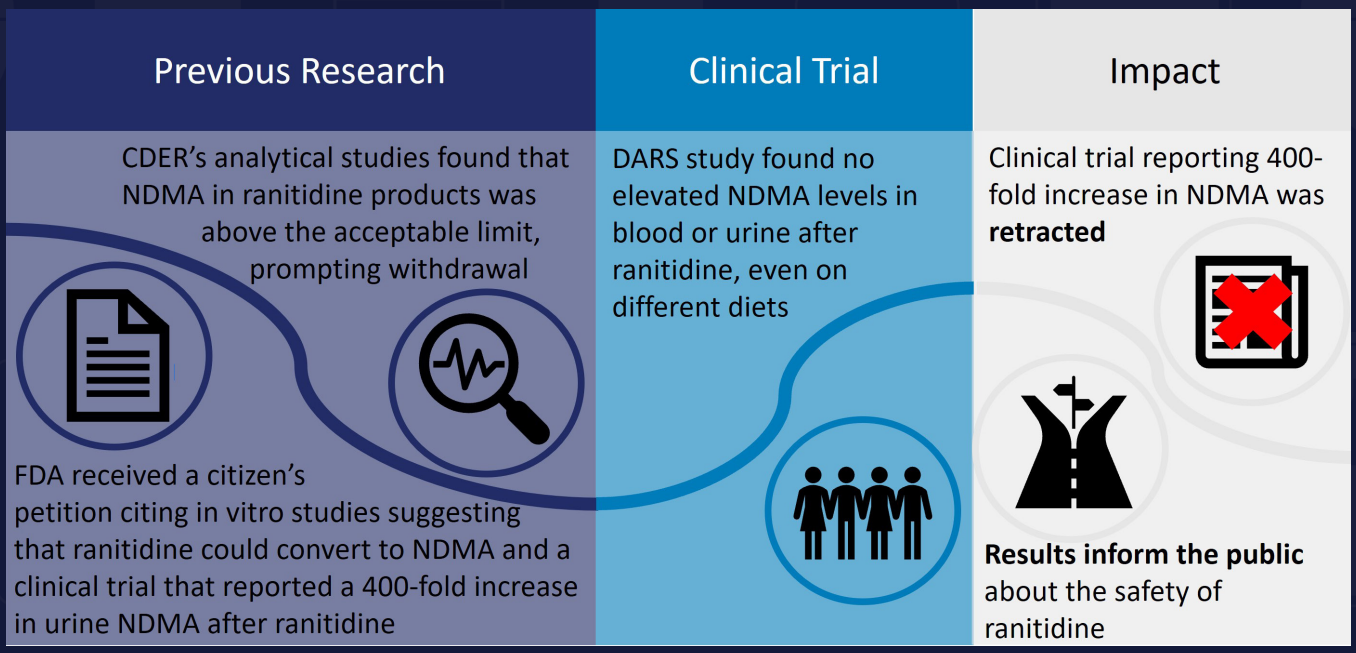
NOTABLE REFERENCES

DARS Publications
Webinar
Questions and Answers for ICH E14/S7B

10 Years of DARS

A Rapid Response to NDMA: Ensuring the Rigor of Regulatory Science

FDA received a citizen's petition indicating that high levels of n-nitrosodimethylamine (NDMA), a probable human carcinogen, had been found in ranitidine products. In response, DARS performed a rigorous, randomized, double-blind, placebo-controlled trial with a sensitive analytical method and found no evidence of elevated NDMA levels in urine or plasma. The results from the DARS study and additional in vitro studies conducted by CDER do not support the conclusion that ranitidine converts to NDMA in humans. These findings will inform whether FDA may consider allowing ranitidine products back on the market if they are shown to be stable with low acceptable amounts of NDMA that do not increase over time during storage.



NOTABLE REFERENCES

DARS Publications
FDA Grand Rounds Presentation
Spotlight on CDER Science

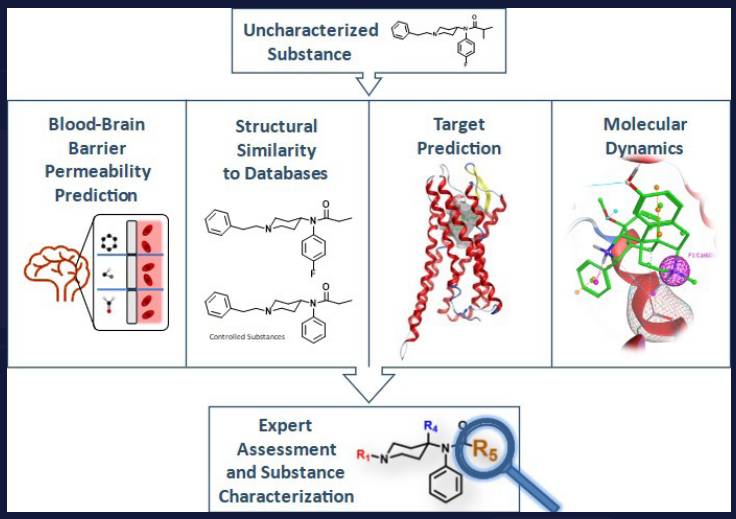
10 Years of DARS

Applied Regulatory Research to Address the Ongoing Opioid Crisis

Prescription opioid analgesics 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. In support of the Agency's efforts, DARS uses its diverse expertise to help fight this public health crisis.

Structure-Based Evaluation of Emerging Drug Threats

DARS developed and employed a rapid computational approach to assess the abuse potential of substances with limited pharmacology information available. The Public Health Assessment via Structural Evaluation (PHASE) methodology predicts the biological function of substances based on chemical structure. As an example, DARS assessed kratom alkaloids, which was highlighted by then-FDA Commissioner Scott Gottlieb in a statement about kratom's potential for abuse, addiction, and serious health consequences.

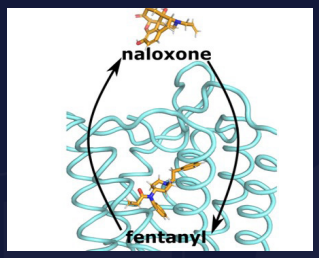


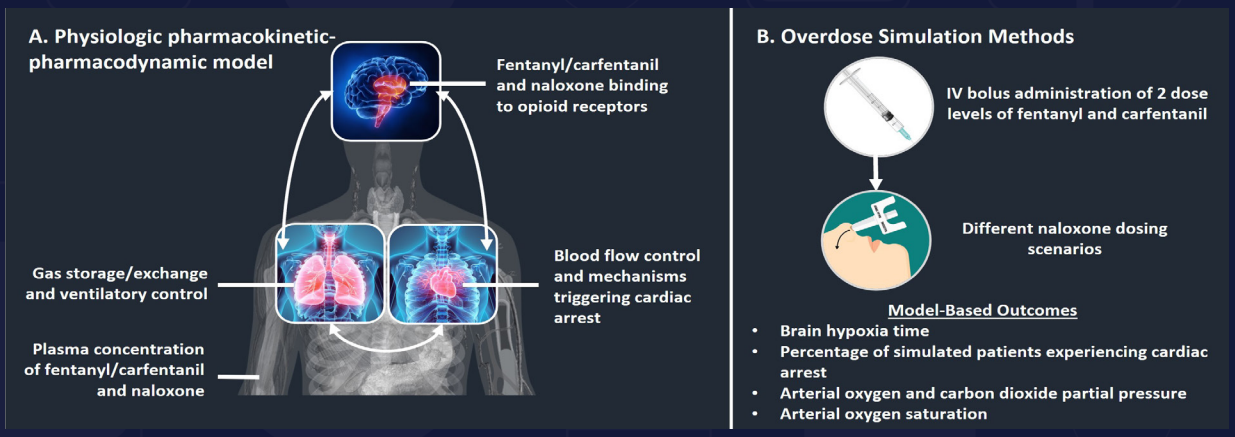
Clinical Trials for Assessing Opioid Safety

FDA issued a warning about the increased risk of decreased breathing when combining opioids with benzodiazepines. Following the warning, DARS received a consult request concerning the potential for drug-drug interactions between opioids and drugs that might be co-prescribed in place of benzodiazepines. DARS developed and used a nonclinical 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 breathing under higher carbon dioxide conditions. Compared to oxycodone alone, the selective serotonin reuptake inhibitor (SSRI) paroxetine in combination with oxycodone decreased breathing. 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 breathing.

Translational Research to Optimize Naloxone Dosing in the Community Setting

DARS is conducting laboratory, computational, and clinical research to optimize the use of existing opioid antagonists (naloxone) and to advance drug development tools for new opioid antagonists. DARS, in collaboration with the University of Maryland, applied an advanced computer modeling method called metadynamics to elucidate how fentanyl binds to the opioid receptor. This new method was also applied to a newly identified opioid that emerged from illegal markets, helping to inform overdose prevention strategies.





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

DARS additionally conducted a clinical trial on the pharmacokinetics of naloxone following repeat administration. These findings have been combined with the computer model above to optimize naloxone dosing strategies.

NOTABLE REFERENCES

DARS Publications
Spotlight on CDER Science
FDA Grand Rounds Presentation

2023 Accomplishments: A Framework for Nitrosamine Safety Assessment

Nitrosamine drug substance-related impurities (NDSRIs) are a class of nitrosamine impurities (which are probable human carcinogens) that have been identified in many drug products. These impurities share structural similarity to the active pharmaceutical ingredient (API) and may be formed through nitrosation of the API. NDSRIs may lack carcinogenicity and mutagenicity study data, which makes it challenging to determine an acceptable intake limit. Therefore, it was essential to establish a risk assessment strategy for potential nitrosamines in pharmaceutical products that may contain these impurities.

DARS led a team of scientists to create the Carcinogenic Potency Categorization Approach, which enables manufacturers and applicants to identify the appropriate recommended acceptable intake limits for NDSRIs and facilitates development of methods for confirmatory testing. This approach uses structure-activity relationships and the presence of certain structural features to generate a prediction of carcinogenic potency to identify a recommended acceptable intake limit.

On August 7, 2023, FDA published a new regulatory guidance that provides drug manufacturers and applicants with a recommended framework for a risk-based safety assessment of NDSRIs, with a main component of the framework being the Carcinogenic Potency Categorization Approach created by DARS.

> "It has been an exciting journey over the last 10 years seeing our foundational regulatory research in (quantitative) structure-activity relationship modeling translate into deliverables that have become a standard part of regulatory review and guidance. It's rewarding to be a part of something so impactful."

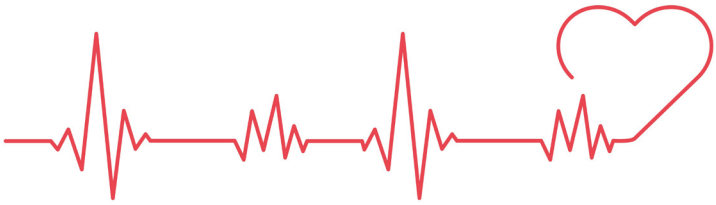
Dr. Naomi Kruhlak
DARS Computational Toxicology Consultation Service Lead

NOTABLE REFERENCES

FDA Guidance: Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)

2023 Accomplishments: Cardiac Safety for Peptides and Proteins

The current strategies for cardiac safety assessment, as presented in the International Council of Harmonisation (ICH) S7B and E14 guidelines, were designed for small molecules and captures the risk of small molecule-mediated delayed repolarization (QT prolongation on the electrocardiogram) and abnormal heart rhythms. Given the increased number of new types of therapies being developed, including peptides, proteins, and oligonucleotides, DARS compiled information from submissions to the FDA on these products to understand whether the current nonclinical strategies covered in ICH S7B and clinical methods described in ICH E14 are adequate for these products.



Results of this research effort showed that ICH S7B results do not predict QT prolongation potential of these products. The results supported the FDA not recommending the dedicated QT studies for peptides comprised of naturally occurring amino acids. This recommendation is reflected in the Clinical Pharmacology Considerations for Peptide Drug Products Guidance for Industry.

NOTABLE REFERENCES

FDA Guidance: Clinical Pharmacology Considerations for Peptide Drug Products

Publication

2023 Accomplishments: Modeling Opioid Antagonist Effects

DARS applied a computer model to provide support for the approval of the first intranasal nalmefene product. The model addressed three key questions: the onset of action, need for repeat dosing, and the capacity to prevent the patient from re-entering an overdose state from residual opioids in the body.

The model has been applied to other scenarios, such as studying the effects of opioids in children and alternative opioid antagonist dosing strategies. Further, the model also provided support for a 10 mg naloxone autoinjector that is being used by the Department of Defense.

NOTABLE REFERENCES

DARS Review
Publication
Regulatory Science in Action

Additional 2023 Highlights

Enhancing the Safety of Opioids and Overdose Reversal Agents

In addition to the advancements previously discussed, 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.

Advancing Alternative Methods to Animal Testing

A public workshop to improve complex in vitro model development was held in September 2023 in conjunction with the Critical Path Institute's Predictive Safety Testing Consortium. Attendees discussed model standards and features to improve performance of complex in vitro models as tools for drug development and regulatory assessment.

Understanding Drug-Drug Interactions

Multiple in vitro studies are underway to evaluate transporter-based drug interactions. Additionally, DARS is conducting a literature review to support internationally harmonized guidelines for evaluating drug interactions.

(Q)SAR Consults

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 17 chemical structures on average per week.

NOTABLE REFERENCES

DARS Overview Article
DARS 2023 Publications
Podcast: Pharmacodynamic Biomarkers for Biosimilars
Spotlight on CDER Science: Pharmacodynamic Biomarkers
Complex In Vitro Model: Qualification Framework Public Workshop

10 Years of DARS: By the Numbers

Publications

330+

Publications Citing DARS Work

4600+

New Drug Applications Evaluated

620+

Generic Drug Applications Evaluated

1600+

Trainees

150+

> “Translational science allows us to overcome urgent public health needs to generate solutions that can be applied to advance drug safety and efficacy through a broad range of research initiatives.”
>
> Dr. Ashok Krishna
> DARS Biologist

Looking Forward: The DARS Strategic Plan

At the end of 2022, after conducting interviews with internal and external stakeholders, DARS finalized a 3-year strategic plan and roadmap. The DARS Strategic Plan seeks to set standards for high-quality applied research and build a sustainable infrastructure to support that quality by:

SETTING THE BAR HIGH — Establish standards for high quality applied research

CULTIVATING A PLACE FOR SUCCESS — Build a sustainable infrastructure that fosters the quality we seek

MOVING THE NEEDLE — Define the tasks needed to get us closer to meeting our goals

> "It has been my privilege and pleasure to be a part of DARS since its inception when it was a research group with potential to its present state as a recognized solver of regulatory challenges. The next ten years holds even greater promise!"

Dr. Rodney Rouse
DARS Deputy Division Director

INITIATIVES THAT PROPEL US

Evaluate Successful Projects	Apply Proven Processes	Mentor Future Leaders	Open New Resource Channels
Evaluating key components of successful projects harnesses the strategies that work optimally, ultimately fueling future successful endeavors.	Implementing industry-proven processes ensures that research at DARS is high-quality with a high success rate and relevant to industry needs.	Growing future leaders brings novel ideas and creativity to the forefront of high-impact research guided by high-impact leaders.	New partnerships and better communication ensure DARS research efforts are efficient, effective, and supported by an abundance of resources.

Contact Us

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2023 DARS Overview Publication

DARS Website

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