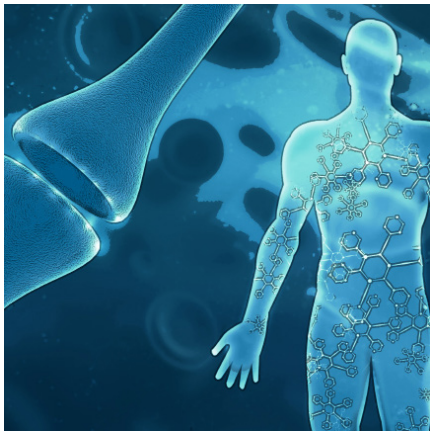
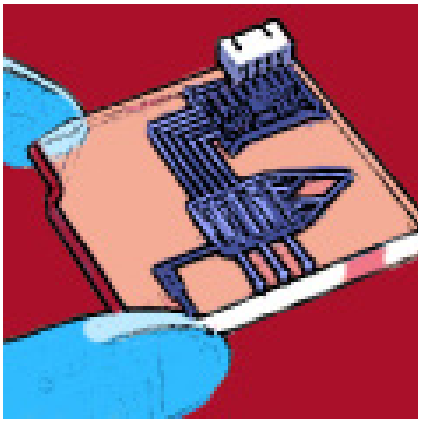
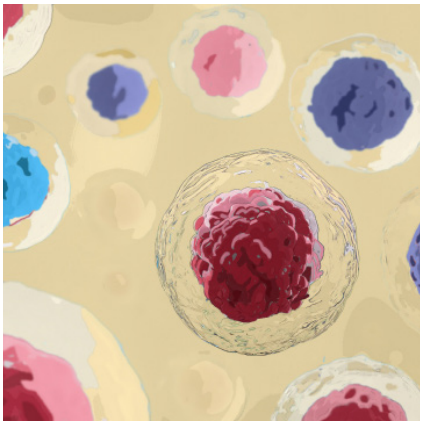
FDA U.S. FOOD & DRUG ADMINISTRATION

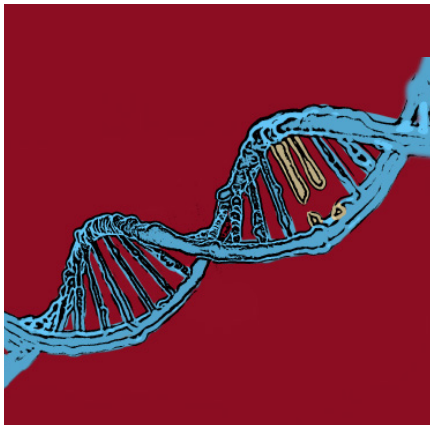
Division of Applied Regulatory Science

2021 Annual Report









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

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Director's MESSAGE

The Division of Applied Regulatory Science (DARS) is unique in that it combines multidisciplinary staff with infrastructure to rapidly conduct laboratory, computational and clinical studies on demand for emergent regulatory and public health questions. DARS staff are nimble, conducting applied research and performing regulatory review consults. DARS is often consulted and takes on projects for some of the most challenging questions the Agency faces.

In 2021, DARS staff engaged stakeholders in collaborative, mission-critical research and review activities related to the safety and effectiveness of COVID-19 therapies, widely-used over-the-counter drugs such as ranitidine and sunscreen, opioids and opioid reversal agents. Additional projects focused on medications for all ages, including pediatrics and geriatrics, and rare diseases.

DARS staff advanced the science, policy and regulatory application of laboratory, computational and clinical drug development tools both at FDA and internationally. For example, DARS is leading the development of an International Council for Harmonisation (ICH) regulatory guideline for cardiac safety and convened a public workshop on pharmacodynamic biomarkers for biosimilars, bringing together international stakeholders.

I am humbled by the dedication of DARS staff and all they have accomplished in advancing public health in 2021 despite limitations put in place by the pandemic. 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 2021 despite the challenges brought on by the pandemic.

54 Applied research projects

41 Presentations delivered

22 Manuscripts published

15 Posters presented

32 Collaborations across 5 countries

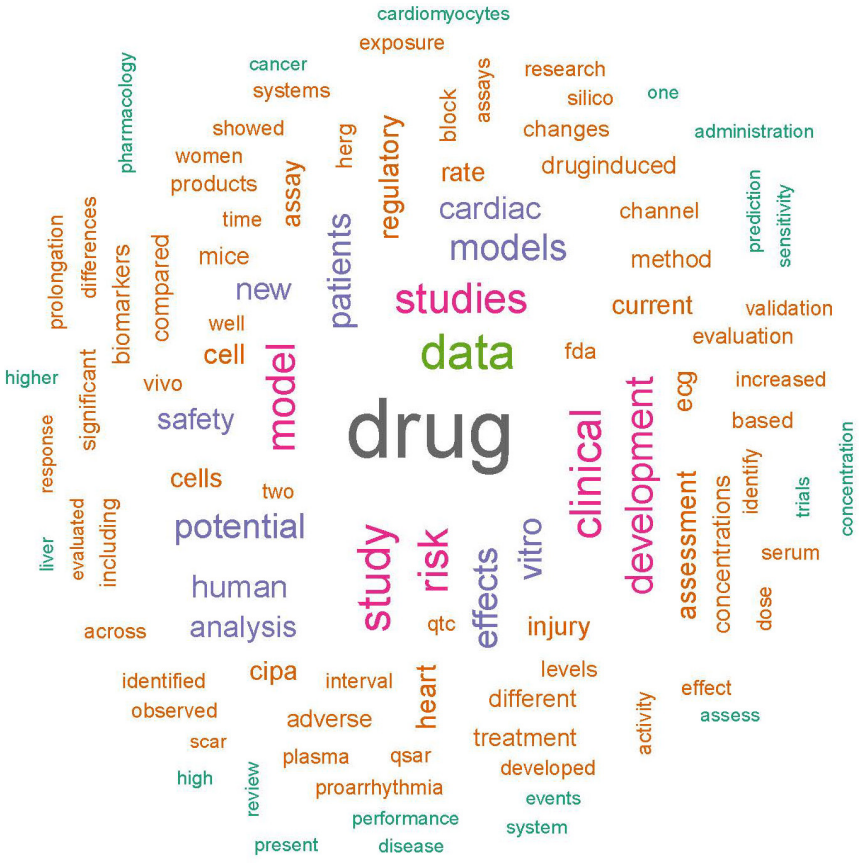
- **13** Research Collaboration Agreements
- **2** Cooperative Research and Development Agreements
- **17** Material Transfer Agreements

Applied Research

OVERVIEW

DARS comprises scientific thought leaders with decades of cumulative experience across the translational research spectrum. This includes 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.

As such, DARS is uniquely positioned to conduct best-in-class, mission-critical research that advances the regulatory evaluation of FDA products. The select projects in the following pages of this report demonstrate the impact of DARS on all aspects of regulatory science, including drug safety, clinical pharmacology, and emerging public health issues.



Responding to Emergent REGULATORY AND PUBLIC HEALTH QUESTIONS

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 evaluating the safety of widely-used over-the-counter drugs.

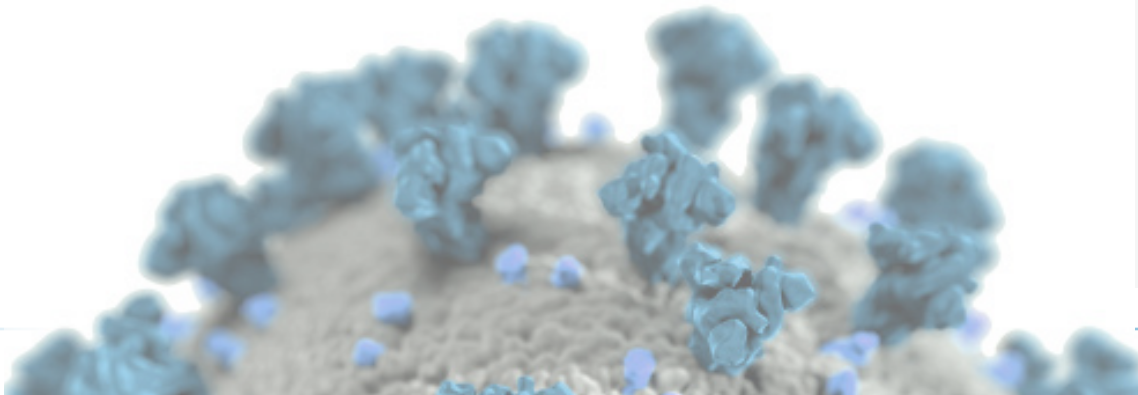
COVID-19

Mechanistic COVID-19 Modeling

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

DARS COVID-19 Regulatory Consults and Reviews

DARS has performed multiple reviews of products related to COVID-19. Recently, a DARS review of remdesivir and its metabolites found they were structurally similar to drugs that are associated with renal and hepatic toxicity. Potential risk of these events is now found in remdesivir's labeling.



EVALUATING THE SAFETY OF WIDELY-USED OVER-THE-COUNTER DRUGS

Does the Heart Burn Medication Ranitidine Convert to a Probable Carcinogen in Humans?

FDA received a citizen petition which proposed the common over-the-counter medication ranitidine could convert to a probable human carcinogen (NDMA) in humans.

In response, **DARS conducted a randomized, placebo-controlled clinical trial** with a sensitive analytical method to measure NDMA in urine and blood. The DARS study, **published in** JAMA, found no evidence of elevated NDMA content in the urine or blood after participants were given ranitidine.

The results from the DARS clinical trial and additional in vitro studies (published in JAMA Network Open) 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 (see Spotlight on CDER Science article and FDA Grand Rounds presentation).

Are Sunscreen Active Ingredients Absorbed?

Pertaining to sunscreens (also a type of widely used over-the-counter product), historical assumptions posited that the active ingredients in sunscreens were not absorbed. While new data showed that sunscreens were absorbed, the studies necessary for addressing this absorption issue were not pursued until DARS initiatives led the way.

DARS conducted 2 clinical trials, both published in JAMA, that confirmed that sunscreen active ingredients can be absorbed and showed the feasibility of studies that FDA was requesting from industry.

Relevant publications

RANITIDINE

Florian et al. JAMA 2021, 326:240-9.

Gao et al. JAMA Network Open 2021, Epub.

Strauss et al. JAMA 2021 23;326:2077.

SUNSCREEN

Matta et al. JAMA 2019, 321:2082-91.

Matta et al. JAMA 2020, 323:256-67.

Califf et al. JAMA 2019, 321:2077-9.

Abbasi. JAMA 2020;323:1431-2.

Strauss et al. JCO Oncol Pract. 2020, 16:436-8.

Pili et al. J Chromatogr B 2021, 1169:122615.

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.

OPIOID SAFETY AND OPIOID REVERSAL AGENTS

Prescription opioids are powerful pain-reducing medications that have both benefits as well as potentially serious risks. One of FDA's highest priorities is advancing efforts to decrease the risk of opioids.

Relevant publications

Vo et al. Nature Commununi-cations 2021, 12:984.

Xu et al. Toxicological Reports 2020, 7:188-197.

Xu et al. Clinical and Translational Sciences 2021, 14:2208-19.

Clinicaltrials.gov links for ongoing clinical trials

- NCT04310579
- NCT04764630
- NCT05168501

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 the medications were given alone and in combination with an opioid. These results were published and informed the design of a clinical trial being conducted by DARS. These studies will inform what, if any, safety actions may need to be taken for certain medications.

Optimizing Opioid Reversal Agents for Use in a Community Setting

Many opioid overdose deaths are attributable to the synthetic opioid fentanyl. DARS conducted computer simulations of how fentanyl binds to the opioid receptor in order to understand why fentanyl may be especially deadly (Nature Communications).

In work on opioid reversal agents, DARS is conducting:

- Combined cellular and computer modeling studies for fentanyl and multiple fentanyl-related opioids to predict the amount of naloxone required to rescue patients from overdoses.
- A clinical trial with different combinations of doses of intranasal naloxone to optimize the use of naloxone in a community setting.

These results will inform on the optimal use of naloxone in the community setting. In addition, DARS's studies are informing how to design feasible and efficient clinical trials to bring new opioid reversal agents to the market.

PEDIATRICS, GERIATRICS AND DRUG LABELING

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.

Drug Labeling for Older Adults

As older adults may be excluded from clinical trials, drug information for these patients, including adverse events, dosing, and pharmacokinetics, may not be available in the FDA product label.

DARS evaluated consistency with the **2020 draft guidance for geriatric information in drug labels** and found that many labels were not consistent with FDA recommendations. **The data generated from this project will inform regulatory review practices for drug labeling.**

Drug Overdose Labeling

DARS is using natural language processing to identify information of interest from drug labels.

Drugs from 10 drug classes highly associated with drug overdose fatalities are being evaluated with this tool to identify labels with potentially outdated overdose treatment recommendations.

This is being used to inform potential updates to the overdose section of drug labeling.

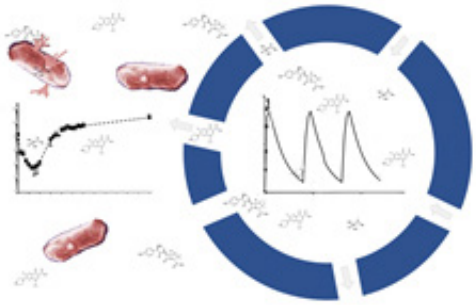
Relevant publications

FDA Reauthorization Act of 2017 (FDARA) Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs

Molecular Targets in Cancer Drug Development: Presentation by Dr. Gregory Reaman, FDA Oncology Center of Excellence

ANTIBIOTIC RESISTANCE AND DRUG-DRUG INTERACTIONS

Antibiotic Resistance



DARS developed a cell-based method to measure the rate at which antibiotic resistance appears. This hollow fiber bioreactor system administers drugs to cells using human pharmacokinetic profiles to identify drug combinations that reduce the development of resistance.

Next-generation sequencing is also being used to investigate the genetic and epigenetic biomarkers of antibiotic resistance and to investigate the effects of combinations of oral antibiotics on bacterial genomes and the gut microbiome.

Drug-Drug Interactions

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

P-glycoprotein efflux transporter (P-gp): DARS is studying if differences exist between the 3 different cell lines used to assess medication interactions with P-gp.

Uridine diphosphate glucuronosyltransferases (UGTs): DARS reviewed drug applications and the scientific literature to compile data for recommendations on standardizing UGT-based DDI studies.

Cytochrome P450: DARS is developing a Structure-Activity Relationship (SAR) model to help identify mechanism-based structural alerts in a metabolite for CYP inhibition studies.

CYP2C9: DARS is studying how the organic anion transporter 2 could affect CYP2C9 DDI studies. Studies suggest it metabolizes warfarin and tolbutamide, which are used in CYP2C9 DDI studies.

Relevant publications

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

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

Xu et al. BMC Genomics 2020, 21:263.

Lee et al. Adv Drug Deliv Rev 2017, 116:100-18.

Volpe et al. Curr Drug Metab 2019, 20:1041-43.

Volpe et al. J Pharm Sci 2018, 107:2983-91.

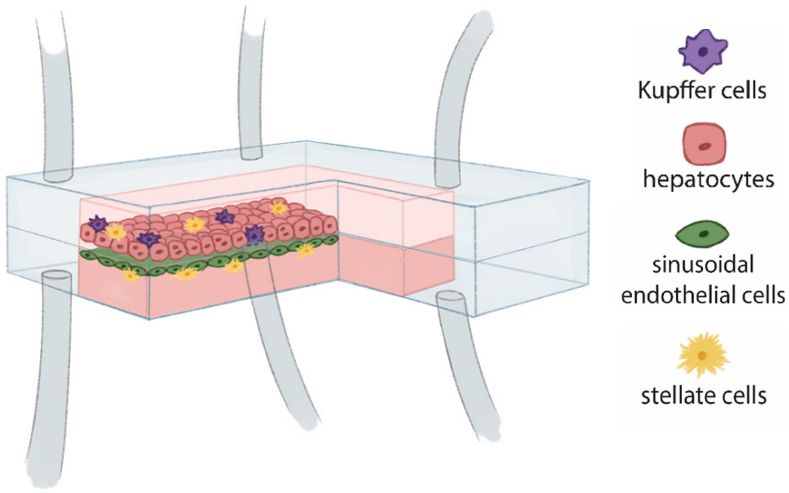
Younis et al. J Clin Pharmacol 2019, 59:1035-43.

MICROPHYSIOLOGICAL SYSTEMS AND INDUCED PLURIPOTENT STEM CELLS

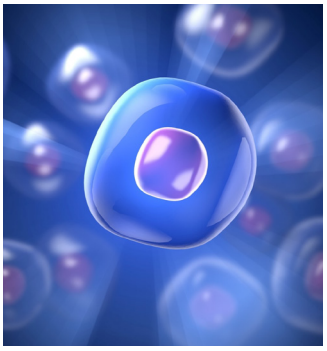
Liver Microphysiological Systems

Liver microphysiological systems (MPSs, also known as organ-on-a-chip) were introduced over 10 years ago as promising tools for predicting liver drug effects. Yet MPSs are still not routinely used in regulatory applications, in part due to a lack of criteria for ensuring reproducibility of results.

DARS characterized a liver MPS with regards to reproducibility of toxicity, metabolism, and drug distribution results. Results indicate that the liver MPS can be used reproducibly in general drug evaluation applications. MPSs give drug developers another tool to test new therapies for patients with unmet needs.



Human Induced Pluripotent Stem Cells



Human induced pluripotent stem cells (iPSCs) are cells created in the lab. These cells can be any cell type found in the body, including heart and liver. Using iPSC-engineered heart cells, heart effects associated with different medications can be predicted as well as a medication's effect on the heart of an individual patient based on their specific genes. DARS is also studying iPSC-engineered liver cells.

DARS is studying how well these laboratory engineered heart and liver cells predict a medication's effect in people and what standards are needed for them to be reproducibly used in regulatory applications.

Relevant publications

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

Ribeiro et al. Clin Pharmacol Ther 2019, 106:139-47.

Dame et al. Exp Biol Med 2021, 246:317-31.

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

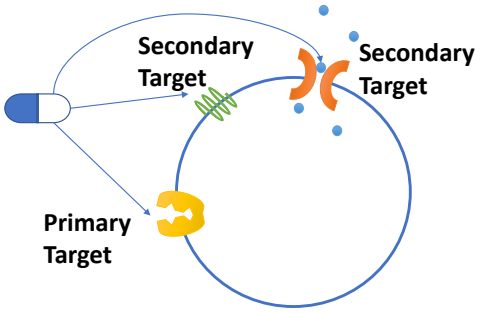
Guth et al. Front Pharmacol 2019, 10:884.

Maddah et al. J Pharmacol Toxicol Methods 2020, 105:106895.

Ribeiro et al. Front Pharmacol 2019, 10:934.

SAFETY PHARMACOLOGY AND TOXICOLOGY

Analysis of Secondary Pharmacology Assays



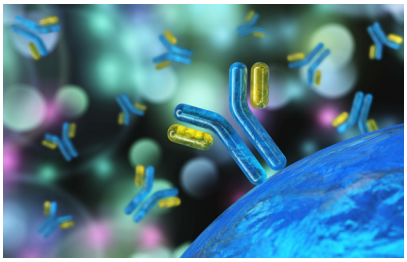
Secondary pharmacology assays are cell-based studies that can identify potential safety issues before entering human clinical trials. However, there is little guidance on which targets should be studied and how the study results should be communicated to FDA.

DARS evaluated 226 studies submitted by pharmaceutical companies and created a database for reviewers.

Results from this study and an ongoing evaluation will inform the best methods for communicating study results and evaluate the need for a standardized list of drug targets for testing.

Immune Mediated Adverse Events

While significant progress has been made in engineering biologic drugs, 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.

Relevant publications

Dodson et al. J Pharmacol Toxicol Methods. 2021 Sep-Oct;111:107098.

Weaver et al. Toxicol Sci 2019, 169:194-208.

Yan et al. Transl Res 2019, 210:43-56.

Yan et al. Toxicol Appl Pharmacol 2019, 372:57-69.

COMPUTATIONAL PHARMACOLOGY AND TOXICOLOGY

(Q)SAR Model Development

DARS is developing computational models that use chemical structure to predict drug adverse outcomes, also known as (Quantitative) Structure-Activity Relationship [(Q)SAR] models. Models being developed include:

- **Blood brain barrier:** Predicts the potential for a drug to cross the blood-brain barrier through permeation or interaction with transporters.
- **Cardiotoxicity:** Updating an existing model using a larger number of drugs and drug classes. The model will provide predictions based on subtypes of cardiac side effects.

Impact of Expert Knowledge on Model Predictions

The current international guideline (ICH M7 [R1]) recommends using both (Q)SAR models and scientific expertise to assess how likely a drug impurity may lead to genetic mutations.

DARS conducted a study to evaluate whether expert review was always needed or for only certain cases. Decreasing the need for expert review would make the review process more efficient.

Evaluating Nitrosamine Safety

DARS collaborated on the development of a computational method to identify comparators to nitrosamine drug substance-related impurities using chemical structure. This enables the evaluation of these impurities and provides information to support its regulatory limit in a drug product without laboratory toxicology data about the specific impurity. Results are being used to inform international harmonized policy for nitrosamine safety with regulatory authorities worldwide.

Quantitative Systems Pharmacology (QSP) Modeling

QSP is a computational model that characterizes biological and pharmacological systems. **DARS is evaluating potential roles for QSP modeling to inform regulatory decision making.**

Additionally, a database of QSP submissions was created to better understand current QSP modeling practices and identify opportunities for QSP in drug development.

Relevant publications

(Q)SAR

Amberg et al. Mutagensis 2019, 34:67-82.

Hasselgren et al. Regul Toxicol Pharmacol 2020, 118:104807.

Hsu et al. Regul Toxicol Pharmacol 2018, 99:274-88.

Jayasekara et al. Regul Toxicol Pharmacol 2021, 125:105006.

Landry et al. Regul Toxicol Pharmacol 2019, 109:104488.

QSP

Bai et al. CPT Pharmacometrics Syst Pharmacol 2021, 10:1479-1484.

Bai et al. CPT Pharmacometrics Syst Pharmacol. 2020 Dec;9:675-677.

Bai et al. AAPS J. 2021 Apr 30;23:60.

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 biosimilars.

Selected Generic and Biosimilars ACTIVITIES

Immunogenicity of Complex Generics and Biosimilars

Impurities 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 biosimilars.

Bioequivalence of Intravitreal Implants

DARS, in collaboration with the Office of Generic Drugs, conducted studies to assess the ability of systemic drug concentrations to demonstrate the bioequivalence of extended-release ocular implants for the anti-inflammatory drug, dexamethasone.

Injectable Delayed-Release Generic Drugs

DARS is studying the ability of a computational model to design bioequivalent (and non-bioequivalent) 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.

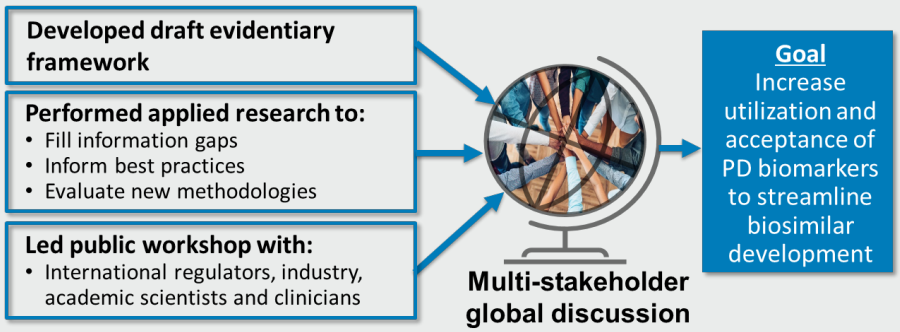
EFFICIENT BIOSIMILAR DEVELOPMENT AND APPROVAL

Advancing the Use of Biomarkers to Streamline Biosimilar 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 development and approvals by advancing the use of pharmacodynamic (PD) biomarkers.

- Developing an evidentiary framework to advance the use of PD biomarkers for biosimilars. A draft version was presented at a recent DARS-led public workshop.
- Performing targeted and applied studies to fill information gaps, inform best practices and evaluate new methodologies, which can be used to refine evidentiary considerations, policy and guidance.



In support of FDA's Biosimilars Action Plan, DARS conducted clinical trials and laboratory studies on diverse biological products to:

- Define best practices on characterizing PD biomarkers for different classes of biological products and types of PD biomarkers to develop general considerations that can be applied to all types of biomarkers for biological products.
- Explore the use of new technologies to identify PD biomarkers or assess multiple biomarkers, such as using proteomics, which can analyze > 7,000 proteins in the blood simultaneously.

Relevant publications

Li et al. Clin Pharmacol Ther 2020, 107:40-2.

Wang et al. Biomark Med 2019, 13:805-9.

DARS-led Public Workshop on Pharmacodynamic Biomarkers for Biosimilar Development and Approval

FDA Biosimilars Action Plan

ClinicalTrials.gov Links to DARS Ongoing Clinical Trials

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 Guideline ACTIVITIES

Drug Development Tools

- DARS leadership serves on the Agency's Drug Development Tools (DDT) Committee, which makes decisions regarding **DDT qualification submissions**.
- DARS staff serve as expert reviewers for DDT qualification submissions.

Drug-Drug Interactions

DARS supports FDA's drug-drug interaction guidance activities, including for the new ICH Guideline:

- Supporting development and publication of final FDA guidance on **in vitro** and **clinical** drug-drug interaction studies.
- Supporting development of an International Council for Harmonisation (ICH) drug-drug interaction guideline, **M12**.

Computational Toxicology

DARS contributed recommendations and regulatory language for the following:

- ICH M7(R2) "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" **Draft Guideline.**
- ICH Q3E EWG "Impurity: Assessment and Control of Extractables and Leachables for Pharmaceuticals and Biologics" **Concept Paper**.

DEVELOPING REGULATORY GUIDANCE: FROM RESEARCH TO PRACTICE

Leading International Guideline Development

Drug development is a global enterprise. It is critical to harmonize requirements among drug regulators globally. The International Council for Harmonisation (ICH) seeks to harmonize requirements for drug development globally.

DARS is serving in the lead (rapporteur) role to update international regulatory guidelines.

Specific Case: Modernizing Cardiac Safety Evaluation

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.

- 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, FDA proposed updating the ICH regulatory guidelines, with a focus on leveraging new technologies and linking the nonclinical and clinical guidelines.
- DARS has led the ICH working group revising the guidelines, releasing a new integrated nonclinical-clinical guideline, and holding a webinar-training with > 2000 attendees from 69 countries.

DARS-led webinar-training on the new draft ICH Guideline with >2,000 attendees from 69 countries (**link**)

Relevant publications

ICH E14/S7B Working Group and Draft Guideline

ICH E14/S7B Draft Guideline Training

Strauss et al. Clin Pharmacol Ther 2021, 109:319-33.

Li et al. Clin Pharmacol Ther 2019, 105:466-75.

Han et al. J Pharmacol Toxicol Methods 2020, Epub.

Tran et al. PLOS One 2020, 15:e0241362.

Vicente et al. Clin Pharmacol Ther 2018, 103:54-66.

Regulatory Consults and REVIEWS

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 assembles 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.

35

Regulatory consults and review team activities completed in 2021

Consults Completed for:

- Office of New Drugs
- Office of Generic Drugs
- Office of Translational Sciences
- Office of the Center Director
- Office of Compliance
- Oncology Center of Excellence
- Office of Surveillance and Epidemiology
- Center for Biologics Evaluation and Research

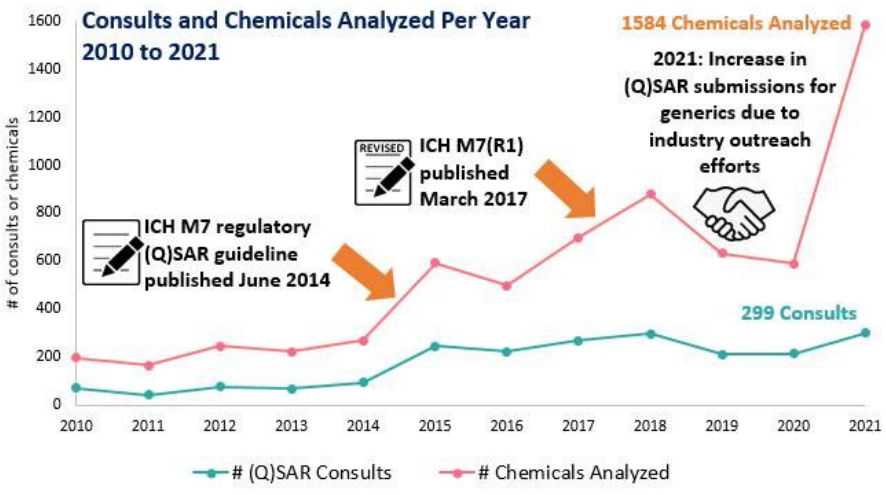
(Q)SAR CONSULTS

FDA requires a rapid and effective way to predict the potential toxicity of drug impurities when faced with data gaps.

In addition to the consults covered above, DARS performs (Quantitative) Structure-Activity Relationship [(Q)SAR] analyses and structure-based searches to predict the genotoxicity and carcinogenicity of drug impurities. In addition, DARS provides consults to assist in the interpretation of (Q)SAR data submitted by pharmaceutical companies. DARS provides (Q)SAR consultations for 30 chemical structures on average per week.

299

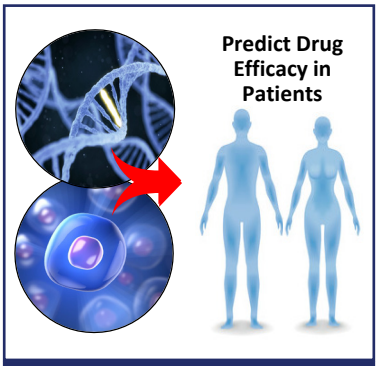
Number of completed consults in 2021



Additional Key INITIATIVES

RARE DISEASES

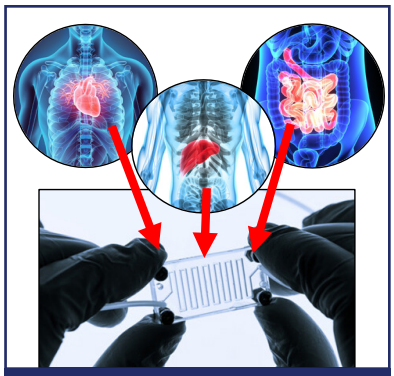
- Rare disease drug development is challenging because of the small number of patients and thousands of genetic variants that may cause a disease.
- DARS is studying the use of cellular models that contain specific genetic variants that cause rare diseases to test if a drug will be effective.
- DARS led the regulatory review of this type of data that was used to expand the approval of drugs for 2 rare diseases: cystic fibrosis and Fabry disease.
- Through further applied research, DARS seeks to broaden the applicability of these



Laboratory Cellular Models to Expand FDA Approvals for Rare Diseases

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.



Human "Organ-on-a-Chip" to Assess Drug Safety, Efficacy or Drug Interactions

Relevant publications

Expanding Approved Patient Populations for Rare Disease Treatment Using In Vitro Data

Advancing Translational Models & Tools into the Drug Review Process

Characterizing the Reproducibility of Microphysiological Systems

Advancing Alternative Methods at FDA

CONTACT US

DARS CLOSES THE GAP BETWEEN SCIENTIFIC INNOVATION AND REGULATORY REVIEW.

DARS Team circa 2019, the last time we were all together in-person.

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 of CDER products.

Want to learn more about DARS?

DARS Website

Contact: Rodney.Rouse@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