

CENTER FOR DRUG EVALUATION AND RESEARCH

What's New in Regulatory Science

Issue I- 2026

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Brought to you by the Office of Translational Sciences (OTS) **within the** Center for Drug Evaluation and Research (CDER).

What's New in Regulatory Science is a bi-annual newsletter from the Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research (CDER). It features new developments, opportunities, and initiatives in drug development and regulatory science, with the goal of advancing medical product development.

Please share this message and the sign-up link with colleagues (after providing your email address, select, research, then "What's New in Science and Research at FDA" as the topic area). If you have comments or questions, please contact us at CDEROTSFeedback@fda.hhs.gov.

REGULATORY SCIENCE IN ACTION

CDER 2025 Annual Reports

CDER publishes annual reports that highlight their wide-ranging contributions to FDA's mission of protecting and promoting public health through scientific innovation, regulatory oversight, and policy development. Across the drug lifecycle, CDER offices work to ensure that new, generic, and biosimilar drug products meet rigorous standards for safety, efficacy, and quality. In addition, CDER offices advance regulatory science through innovations in model-informed drug development, real-world evidence, artificial intelligence, and postmarket safety surveillance. Together, these reports reflect CDER's collective commitment to expanding patient access to safe and effective medicines while continuously strengthening the tools, methods, and policies that underpin sound regulatory decision-making.

Division of Applied Regulatory Science 2025 Annual Report

FY 2025 GDUFA Science and Research Report

Office of Clinical Pharmacology 2025 Annual Report

Office of Compliance 2025 Annual Report

Office of Translational Sciences 2025 Annual Report

New Drug Therapy Approvals 2025

Report on the State of Pharmaceutical Quality FY2025

CDER Center for Clinical Trial Innovation (C3TI) Demonstration Program Fosters Early Engagement with Drug Developers on Innovative Clinical Trial Approaches

The CDER Center for Clinical Trial Innovation (C3TI) Demonstration Program provides an opportunity for drug developers to test and scale the integration of innovative approaches to clinical trial design and conduct. In this program, clinical trial sponsors can engage early with CDER review teams and subject matter experts in a structured and direct manner on innovative trial elements.



A key objective of the C3TI Demonstration Program is to share insights related to the innovative elements of selected trials with the broader clinical trial community. To support this goal, participating sponsors and FDA will agree on what aspects of the development program can be shared publicly.

Generally, participating sponsors will be expected to share select details of their clinical trials and the implementation of innovative approaches as the trials progress. This may include updates and insights that focus on general principles and innovative aspects while maintaining the necessary confidentiality of proprietary or sensitive information.

The Demonstration Program accepts projects on a rolling basis and is open to selected sponsors conducting innovative clinical trials under a pre-investigational new drug application (pre-IND) or IND with CDER. These trials should be intended to support new drug approvals or changes to approved drug labeling.

C3TI currently has three demonstration project areas:

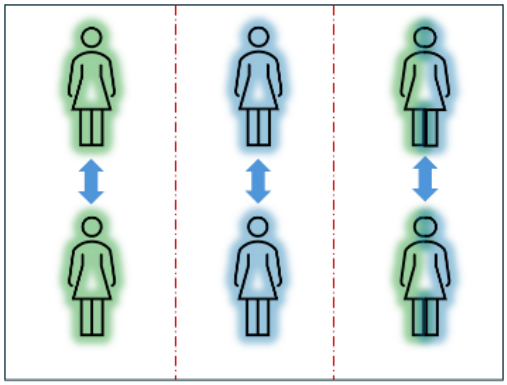
- Bayesian Statistical Analysis
- Selective Safety Data Collection
- Streamlined Trials Embedded in clinical Practice

More information about C3TI and its demonstration program, including eligibility criteria and how to submit a proposal, is available on the C3TI webpage.

Regulatory Science Impact Stories

A Novel Stratum-Specific Trial Design Improves Statistical Power for Rare Diseases with Heterogeneous Clinical Symptoms

Clinical trials for rare diseases face significant statistical challenges: small patient populations limit enrollment and the heterogeneous clinical presentations common to many rare diseases further reduce statistical power by making it difficult to identify a single primary endpoint applicable to all participants. Traditional trial designs either enroll all patients using uniform endpoints regardless of their symptoms or restrict enrollment to patients experiencing all symptoms under investigation — both approaches can substantially limit a trial's power.

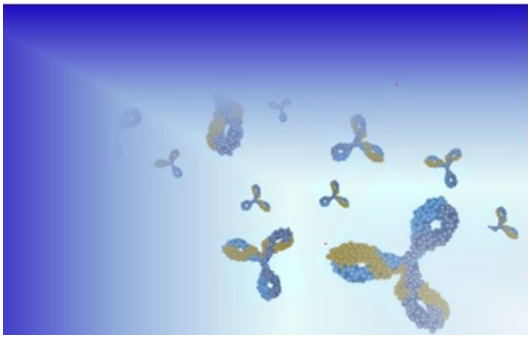


To address these challenges, CDER statisticians developed a novel stratum-specific trial design in which patients are grouped into subpopulations based on the symptoms they experience at baseline, and treatment efficacy is evaluated using only the endpoints relevant to each patient's subpopulation. Using computer simulations, researchers compared this design against traditional global test approaches and found substantial gains in statistical power for a given subpopulation size — meaning fewer total patients are needed to achieve the same level of evidence as a traditionally designed trial. When followed by the Hochberg method for multiple testing correction, the design also maintained reasonable power to draw conclusions about treatment effects on specific symptoms.

The stratum-specific design has important limitations, including a weaker interpretation of significant global test results compared to traditional trials, and an assumption of well-defined, accurately categorized subpopulations at baseline that does not account for patient misclassification or post-randomization symptom changes. Despite these limitations, CDER researchers suggest this framework offers a valuable and flexible paradigm for rare disease drug development, with the potential to support more efficient clinical trials and strengthen the evidence base for regulatory approval of effective therapies. Sponsors are encouraged to explore this design further through FDA's Complex Innovative Trial Design Meeting Program and the LEADER 3D initiative. Learn more.

Comparative Clinical Studies for Assessing the Safety and Immunogenicity of Biosimilars

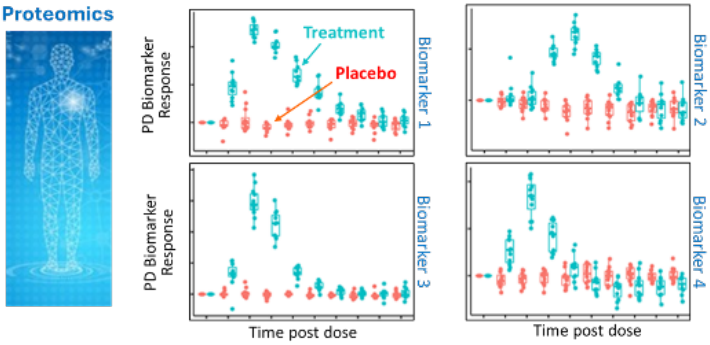
Biosimilars, biological products demonstrated to be highly similar to an FDA-approved reference product with no clinically meaningful differences in safety, purity, or potency, offer a critical pathway to improving patient access to complex and often costly biologic therapies. Demonstrating biosimilarity has historically required both pharmacokinetic (PK) similarity studies, which compare drug exposure over time, and comparative clinical studies (CCS), which evaluate efficacy, safety, and immunogenicity in patient populations often numbering in the hundreds. However, there is growing recognition that CCS are of limited sensitivity for detecting product differences compared to analytical studies, raising questions about the added value of CCS for evaluating relative safety and immunogenicity specifically.



To assess this question, CDER scientists conducted a meta-analysis of data submitted in support of 35 approved biosimilars, all monoclonal antibodies or fusion proteins, comparing the safety and immunogenicity information provided by PK studies versus CCS. The analysis found no statistically significant differences in the risk of anti-drug antibody or neutralizing antibody development between the two study types. While estimated risks for adverse events were generally lower in PK studies than in CCS, overall differences were small and statistically significant only for serious adverse events.

These findings support the conclusion that PK similarity studies, as currently designed, provide comparable descriptive information on immunogenicity and safety to that obtained from comparative clinical studies. This research contributes to the broader body of scientific evidence informing FDA's updated recommendations on the role of comparative clinical studies in biosimilar development, with implications for streamlining development programs and reducing costs without compromising the rigor of biosimilarity assessments. Learn more.

Proteomics-Based Biomarker Discovery: A Systematic Framework to Address Regulatory and Scientific Challenges Across Therapeutic Areas



CDER researchers have developed a structured and systematic framework for biomarker discovery using plasma proteomics

Biomarkers are critical tools in drug development, serving as measurable indicators of biological processes, disease progression, and therapeutic response. Traditional biomarker discovery methods are often limited in scope, relying on single-target, hypothesis-driven approaches that may miss broader patterns of drug response, a particular challenge in complex or rare diseases. To address this, CDER researchers developed a structured, three-phase framework for biomarker discovery using aptamer-based plasma proteomics, a high-throughput method capable of simultaneously measuring over 7,000 proteins in plasma samples.

The framework integrates Discovery, Replication, and Characterization phases, incorporating best practices for study design, data normalization, statistical analysis, and control of technical variability to ensure scientifically rigorous and reproducible results. By capturing comprehensive, pathway-level biological responses to therapeutic agents, this approach goes beyond traditional single-target methods and is broadly applicable across therapeutic areas and biomarker types, including pharmacodynamic, toxicity, and surrogate markers.

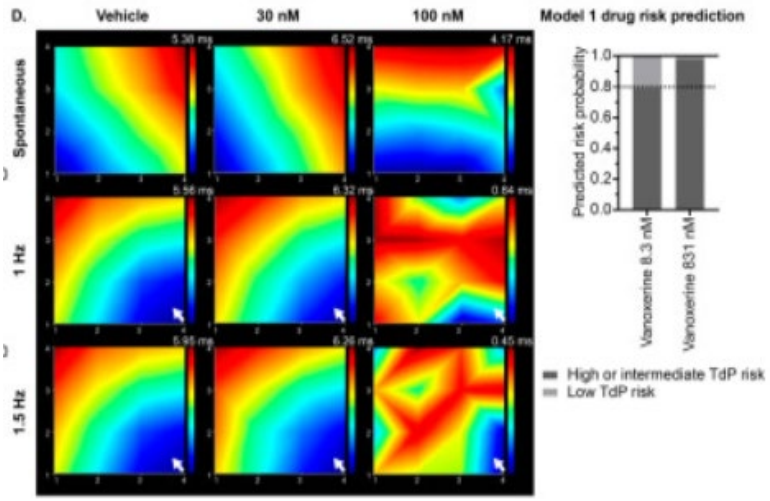
This work advances regulatory science by providing a standardized, reproducible pathway for integrating large-scale omics data into drug development and regulatory evaluation. The framework supports more informed clinical trial decision-making — including dose selection, patient stratification, and endpoint identification — and is especially valuable in rare diseases where patient populations are small and traditional endpoints are difficult to assess. Ultimately, it serves as a model for applying high-dimensional analytical technologies in a manner consistent with FDA principles of transparency, reproducibility, and data integrity. Learn more.

IN PRESS

This section provides highlights of select CDER research recently published in scientific journals.



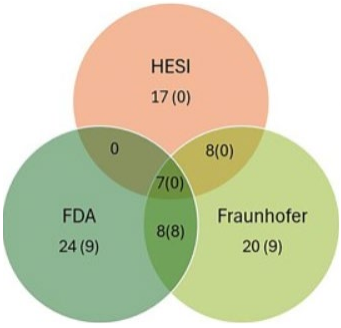
Nonclinical Human Cardiac New Approach Methodologies (NAMs) Predict Vanoxerine-Induced Proarrhythmic Potential



Garcia MI, Bhardwaj B, Dame K, Charwat V, Siemons BA, Goswami I, Ismaiel OA, Mistry S, Feaster TK, Healy KE, Ribeiro AJS, Blinova K. J Cardiovasc Dev Dis. 2025 Jul 26;12(8):285.

Cardiac New Approach Methodologies (NAMs) were evaluated for their ability to detect drug-induced cardiac arrhythmic events that were not identified in nonclinical animal models or Phase I-II clinical trials. More specifically, the NAM utilized human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) and electrophysiological measurements. The drug examined, vanoxerine, has known cardiac risks that were not detected until late-stage clinical trials. In this study, researchers demonstrated for the first time that this compound triggered proarrhythmic events in a human-relevant nonclinical model. These findings demonstrate that this nonclinical cardiac NAM can successfully recapitulate clinical outcomes associated with vanoxerine.

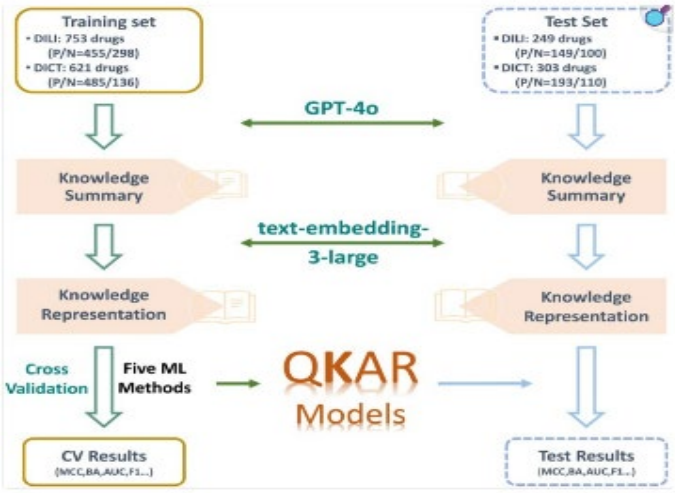
Nitrosamine Ames Data Review and Method Development: Proceedings of a US FDA/HESI Workshop



Atrakchi, Aisar; Puglisi, Raechel; Bercu, Joel; Cheung, Jennifer; Czich, Andreas; Froestchl, Roland; Davis-Bruno, Karen; Heflich, Robert H; Kobets, Tetyana; McGovern, Timothy J; Lynch, Anthony; Selby, Max; Schuler, Maik; Silveira, Gabriela De Oliveira; Vespa, Alisa; Whomsley, Rhys; Chen, Connie L. Mutagenesis. 2026 Jun 27;41(4):225-236.

Due to concerns over the sensitivity of the standard Ames test (OECD Test Guideline 471) in detecting the mutagenic and carcinogenic potential of N-nitrosamines (NAs) — including NA Drug Substance-Related Impurities (NDSRIs) found in marketed pharmaceuticals — the FDA's Center for Drug Evaluation and Research (CDER) Office of New Drugs (OND) and the Health and Environmental Sciences Institute's Genetic Toxicology Technical Committee (HESI/GTTC) co-organized a workshop to discuss optimized Ames test conditions for evaluating NAs and NDSRIs, with sessions addressing key parameters such as metabolic activation methods and tester strain selection. This report summarizes the key takeaways from that workshop.

Beyond QSARs: Quantitative Knowledge-Activity Relationships (QKARs) for enhanced drug toxicity prediction

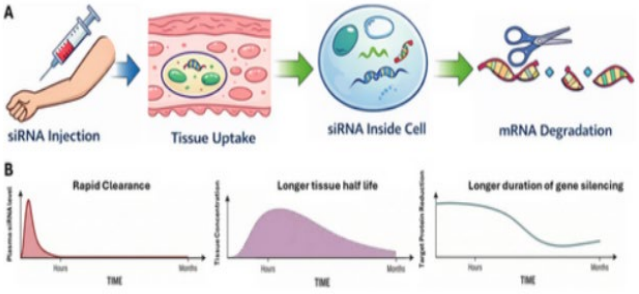


Li, Ting; Qu, Yanyan; Chen, Alexander; Thakkar, Shraddha; Li, Dongying; Tong, Weida. Toxicol Sci. 2025 Dec 1;208(2):269–278.

This study introduces Quantitative Knowledge-Activity Relationships (QKARs), a novel computational framework that predicts drug toxicity using domain-specific knowledge rather than relying solely on chemical structure as traditional Quantitative Structure-Activity Relationships (QSARs) do. QKAR models were developed for two key toxicity endpoints, drug-induced liver injury (DILI) and drug-induced cardiotoxicity (DICT). Leveraging the advances in AI, including text embedding and generative AI, were found to consistently outperform QSARs, particularly in distinguishing drugs with similar structures but different toxicity profiles. The study also explored integrating knowledge-based and structure-based representations (Q(K+S)ARs), demonstrating that QKARs offer a robust and promising alternative to QSARs for enhanced drug toxicity prediction and risk assessment.

Optimizing Oligonucleotide Therapeutics: A Model-Informed Drug Development Perspective

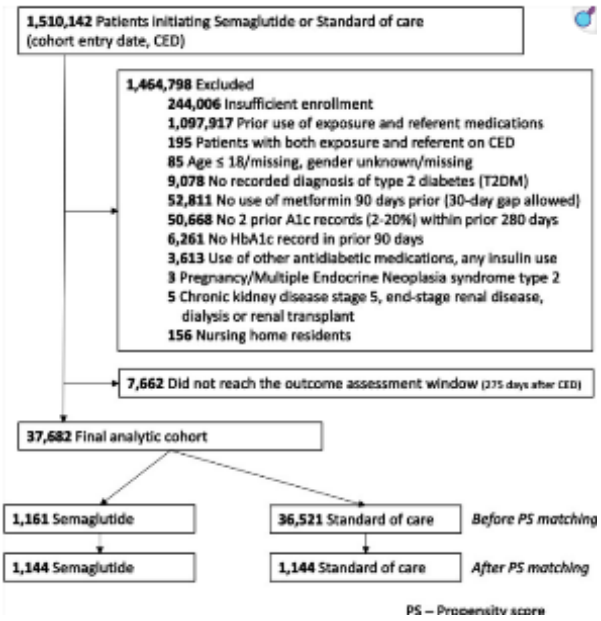
Yuan, Ye; Sharma, Vishnu; Bhattaram, Venkatesh Atul; Pan, Xiaolei; Earp, Justin; Wang, Yun; Liu, Jiang; Zhu, Hao. Clin Transl Sci. 2026 May;19(5):e70570



Oligonucleotide therapies, including antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), and aptamers, present unique drug development challenges, particularly the disconnect between systemic exposure and tissue activity, where these therapeutics are rapidly cleared from circulation yet persist intracellularly with sustained effects, complicating dose optimization and efficacy prediction especially given limited clinical data from rare disease indications. This review examines how Model-Informed Drug Development (MIDD) has emerged as a critical solution to these challenges across FDA-approved oligonucleotide therapies, demonstrating how quantitative modeling has been successfully applied to bridge the PK-PD disconnect, inform endpoint selection for accelerated approvals, guide dosing strategies for general and special populations, and ultimately advance the clinical and regulatory success of this therapeutic class.

Using real-world data to predict findings of an ongoing phase IV trial: glycemic control of semaglutide versus standard of care

Kattinakere Sreedhara S, Schneeweiss S, D'Andrea E, Weberpals JG, DiCesare EC, Patorno E, Tsacogianis T, Bradley M, Concato J, Wang SV. BMJ Open Diabetes Res Care. 2025 Oct 29;13(5):e005180.



Using national claims data (Optum Clinformatics, 2017–2022), this study emulated the design of the ongoing SEPRA trial to compare once-weekly injectable semaglutide against standard-of-care (SoC) medications for glycemic control (A1C <7%) in adults with type-2 diabetes on metformin monotherapy. Among 1,144 propensity score-matched pairs, semaglutide initiators were 30% more likely to achieve glycemic control (RR 1.30, 95% CI: 1.16–1.45) and showed a slightly greater A1C reduction (1.3% vs. 1.1%) compared to SoC, findings that were consistent with interim SEPRA trial results released after the study protocol was preregistered. These results support the value of well-designed, preregistered non-randomized studies using fit-for-purpose real-world data as effective complements to pragmatic randomized controlled trials.

Information about FDA's Regulatory Science Research

FDA's Regulatory Science

Regulatory Science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products. Learn more.

FDA: Overview of our Role Regulating and Approving Drugs | Video Series
FDA oversees prescription, generic, biosimilars, and over-the-counter drugs. Learn more.

CDER Office of New Drugs- Regulatory Science Research
The Office of New Drugs (OND)-led regulatory science research projects are designed to address knowledge gaps identified during regulatory review of investigational or new drug applications. Learn more.

CDER Office of Generic Drugs- Science and Research
The Office of Research and Standards within the FDA's Office of Generic Drugs (OGD) supports the Science and Research program established under the Generic Drug User Fee Amendments (GDUFA). In collaboration with industry and the public, FDA creates an annual list of its regulatory science initiatives on generic drugs. Learn more.

Research Tools and Resources
Developing and sharing knowledge and scientific resources with researchers in the public and private sectors is at the heart of what CDER scientists do. Learn more.

FDA Fellowship Opportunities

FDA Oak Ridge Institute for Science and Education (ORISE) Fellowships

The FDA ORISE program offers college students, recent graduates, postdoctoral researchers, and faculty the opportunity to learn alongside FDA scientists and professionals, contribute to mission-driven research, and build valuable skills and professional connections. Participants will gain hands-on experience that can provide a competitive advantage for future careers in science and public service.

Explore FDA ORISE training opportunities and put your education and talent to work advancing the health and safety of the nation.

The program is administered by Oak Ridge Associated Universities [orau.org] (ORAU) through the Oak Ridge Institute for Science and Education (ORISE) under an agreement between the FDA and the U.S. Department of Energy. Learn more.