U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Office of New Drugs ORISE Fellowship Research Outcomes Report (FY2021)

January 2023

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Background

How does OND use regulatory science research (RSR) to stimulate new drug development?

The Office of New Drugs Research Program (OND-RP) was created in 2019 to foster regulatory science research (RSR). OND plays a proactive role in stimulating drug development by investing in RSR that will address targeted knowledge gaps identified during regulatory review. External stakeholders benefit from OND's RSR activity as project outcomes are used by OND staff to develop or clarify regulatory pathways in areas of unmet need.

Why does OND participate in FDA's ORISE Fellowship Program?

The ORISE Fellowship is a training program for college students and recent graduates. ORISE Fellows participate in mentor-led research projects to gain hands-on experience in the field of regulatory science.

OND's regulatory science research projects address targeted questions and produce outcomes that directly facilitate new drug approvals. This focused approach makes OND's ORISE projects attractive to early career investigators as they typically result in resume-enhancing accomplishments.

Purpose and scope of this report

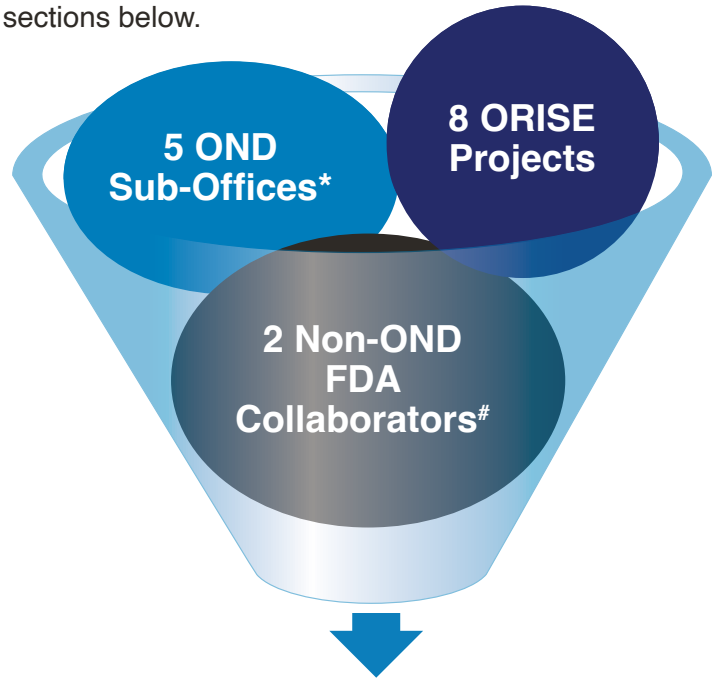
The purpose of this report is to summarize outcomes from OND-funded ORISE fellowships. Outcomes were generated in fiscal year 2021 (FY21).

FY21 Research Outcomes

Outcomes are organized into three categories: external peer-reviewed publications, external presentations, and drug development tools.

External Peer-Reviewed Publications

In FY21, **eight OND ORISE projects** produced 13 publications in peer-reviewed journals. These projects were housed in various OND review divisions, which shows the broad diversity offered in OND's ORISE fellowships. Many of these projects were made possible through FDA collaborations with groups from outside of OND. The top three most cited publications are featured in the snapshots sections below.



13 External Peer-Reviewed Publications

Snapshot: Top Three Most Cited Publications

Bioresorbable scaffold-based controlled drug delivery for restenosis.

Tesfamariam B (2019) J Cardiovasc Transl Res ; 12(3): 193-203

Creatinine-based renal function assessment in pediatric drug development: an analysis using clinical data for renally eliminated drugs.

Zhang Y, Sherwin CM, Gonzalez D, Zhang Q, Khurana M, Fisher J, Burckart GJ, Wang Y, Yao LP, Ganley CJ, Wang J (2021) Clin Pharmacol Ther ; 109(1): 263-9

Public workshop summary: advancing animal models for antibacterial drug development.

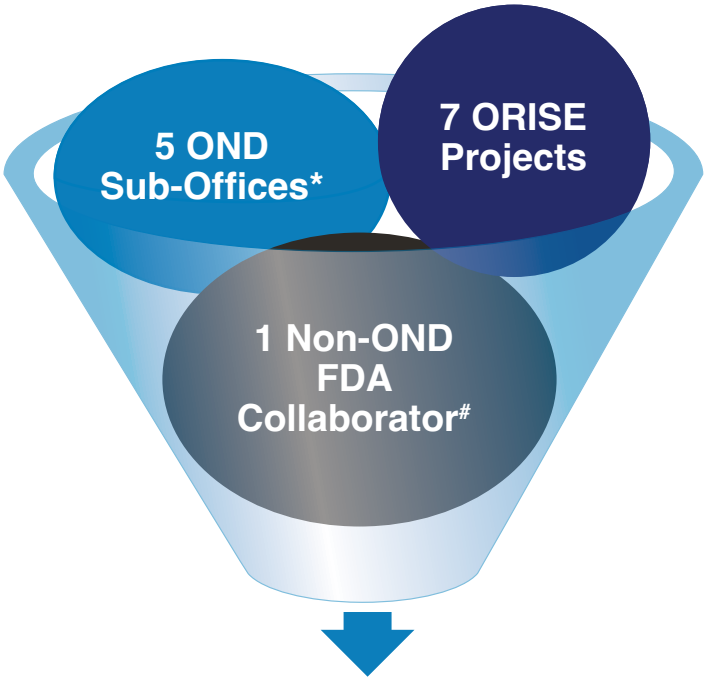
Byrne JM, Waack U, Weinstein EA, Joshi A, Shurland SM, Iarikov D, Bulitta JB, Diep BA, Guina T, Hope WW, Lawrenz MB, Lepak AJ, Luna BM, Miesel L, Phipps AJ, Walsh TJ, Weiss W, Amini T, Farley JJ (2020) Antimicrob Agents Chemother; 65(1) :e01983-20

***OND Sub-Offices include:** Cardiology, Hematology, Endocrinology and Nephrology | Infectious Disease | Immunology and Inflammation | Rare Diseases, Pediatrics, Urologic and Reproductive Medicine | Immediate Office

#Non-OND FDA Collaborators include: CDER Office of Translational Sciences | FDA Oncology Center of Excellence

External Presentations

In FY21, **seven OND ORISE projects** resulted in 17 presentations at external scientific meetings for professional societies. These presentations were significant as they helped OND get feedback from external stakeholders on the progress of our research. The two projects with the highest number of presentations are highlighted below.



17 External Presentations at Scientific Meetings

Snapshot: Projects with the Largest Number of Presentations

Leveraging SEND Datasets for Enhanced Analysis/Visualization – 6 Presentations

Fellow: MD Yousuf Ali, PhD I Mentor: Kevin Snyder, PhD

Evaluating Standard Methods to Analyze and Present Patient Reported Outcome and Other Clinical Outcome Assessment Data – 4 Presentations

Fellow: Meena Murugappan, PharmD, MPH, PhD I Mentor: Vishal Bhatnagar, MD

***OND Sub-Offices include:** Cardiology, Hematology, Endocrinology and Nephrology I Infectious Disease I Immunology and Inflammation I Speciality Medicine I Immediate Office

#Non-OND FDA Collaborator includes: FDA Oncology Center of Excellence

Drug Development Tools

In FY21, OND's ORISE fellowships resulted in **six internal review tools and two external lists** that will be used to facilitate drug development.

Ion Channel Data Standards for Model-Informed Proarrhythmia Risk Prediction Under the Comprehensive in vitro Proarrthymia Assay (CiPA) Initiative

Division of Cardiology and Nephrology (DCN)
Internal review tools

Many drugs have been restricted or withdrawn from the market due to concerns about cardiac safety. Drug-induced cardiac repolarization prolongation and the associated risk of torsade de pointes (TdP), a potentially fatal arrhythmia, are among the most serious adverse effects that can occur. No drugs with unacceptable risk for TdP have reached the market under the current International Council for Harmonisation of Technical Requirements for Pharmaceuticals
for Human Use (ICH) guidelines . The Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative is a is a global collaborative effort between FDA, industry, and academic stakeholders with a goal of developing a new, mechanistic-based method for evaluating cardiac safety. As part of FDA's role in CiPA, DCN established an ORISE fellowship to define data standards and a processing pathway for in vitro multi-ion channel data that will be used to inform an in silico model for proarrhythmia risk assessment.

Outcomes: In FY21, this fellowship produced reports used to train the Interdisciplinary Review Team for Cardiac Safety Studies on best practice assessment under new ICH E14/S7B draft Q&As. In addition, the fellows on this project contributed to the development of data format and analysis tools that were used by staff to inform decisions about the adequacy of datasets submitted in 10+ marketing applications under the ICH E14/S7B draft Q&As as well as for sharing and analyzing data from a multi-year BAA contract including 8 labs (14 drugs per lab).

[1]ICH Guidances: E14: Clinical Evaluation of the QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs and S7B: Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

Identify Challenges and Research Frequently Encountered Issues While Combining Data across Multiple Studies/Sources

Division of Bioinformatics, Research, and Biomarker Development (DBIRBD)
Internal review tool

DBIRBD pursued a project that was intended to provide OND clinical reviewers with an improved ability to detect safety signals in clinical trial datasets. To address this need, DBIRBD hosted an ORISE Fellowship to contribute to the development of FDA Medical Queries, which are standardized groupings of similar adverse event terms. During this work, an integrated adverse event dataset from greater than 5000 clinical trials was developed and used to support the work.

Outcome: Version 1 of the FMQs was successfully completed in FY21. This internal resource creates a regulatory impact by helping OND staff consistently define, categorize, and analyze clinical adverse events reported in marketing applications.

Pediatric Development of Molecularly Targeted Drugs

Office of Oncologic Diseases Immediate Office (OOD IO)
External list

Section 504 of the FDA Reauthorization Act of 2017 (FDARA) required FDA to publish a list of molecular targets that are substantially relevant to the growth or progression of one or more pediatric cancers (the "Relevant Molecular Target List"). OND established an ORISE Fellowship to work with FDA and National Cancer Institute (NCI) staff to contribute to the development of this resource. The current version of the list is available on FDA's website to guide stakeholders regarding which targets may trigger Pediatric Research Equity Act (PREA) requirements for submission of a report of a molecularly targeted pediatric cancer investigation of a new targeted oncology drug or biologic product.

Outcome: In FY21, the Relevant Molecular Target List was used by FDA's Pediatric Review Committee (PeRC) to help inform discussions regarding initial Pediatric Study Plans for over 100 distinct drugs or biologics that had not been previously approved.

Evaluation of Drug Substances for Pharmacy Compounding

Office of Specialty Medicine Immediate Office (OSM IO)
Internal review tool

In 2013, Congress enacted the Drug Quality and Security Act (DQSA) to address gaps in the way compounded medications are prepared and distributed. After this law was passed, CDER began a systematic evaluation of certain bulk drug substances to determine their suitability for inclusion in the 503A and 503B bulks lists. OSM's ORISE Fellows played a key role in compiling nonclinical and clinical data for each of the substances nominated by the public.

Outcome: In FY21, the fellows contributed to the development of an internal job aid "Methodology for Efficient Analysis of Comments to Notice of Pharmacy Compounding Advisory Committee Meeting" and several resources to streamline internal review of compounded drug substances: 1) templates to standardize internal evaluation of bulk drug substances and 2) a database to store information related to evaluations. This database is now used CDER-wide as a central repository for all information related to internal review of bulk drug substances.

DCN Pediatric Database

Division of Cardiology and Nephrology (DCN)
Internal review tool

There has been an increase in pediatric drug development submissions since enactment of the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA). As new therapeutic products are developed, FDA's thinking on pediatric drug development in various therapeutic areas continues to evolve. The Division of Cardiology and Nephrology (DCN) hosted an ORISE Fellowship to contribute to the development of an internal database that would facilitate tracking for pediatric drug development programs in OND. This comprehensive, searchable pediatric database tracks program outcomes, optimizes compliance with PREA, and provides a resource that facilitates drug development for pediatric patients.

Outcome: In FY21, the first prototype of the DCN Pediatric Database was completed. The database captures information on the nature of BPCA and PREA-related commitments, FDA actions, advice related to those commitments, and administrative information. Approaches to complete and further refine the database, and to automate and integrate data retrieval from existing FDA IT systems are currently under development.

Rare Disease Knowledge Management and Characterizing the Impact of the Rare Pediatric Disease Priority Review Voucher

Division of Rare Diseases and Medical Genetics (DRDMG)
Internal review tool

In the PDUFA VI Commitment Letter, FDA agreed to build upon work that will "facilitate the development and timely approval of drugs and biologics for rare diseases, including rare diseases for children." DRDMG hosted an ORISE Fellowship to contribute to the development on an internal dashboard that would facilitate tracking of rare disease clinical development programs. Potential areas of focus include use of biomarkers, non-traditional clinical development programs, use of adaptive study designs, evaluation of novel endpoints, application of new approaches to statistical analysis, and use of FDA's expedited development and review programs (i.e., Fast Track, Breakthrough, Priority Review, and Accelerated Approval).

Outcome: In FY21, the fellow on this project also conducted an analysis of the Rare Pediatric Disease (RPD) Priority Review Vouchers (PRVs) granted for Rare Pediatric Diseases. The information gathered for 19 RPD PRVs from 2014-2019 has added value to ongoing discussions between FDA's Office of Orphan Products Development (OOPD) and CDER's rare diseases subject matter experts.

Development of a Model for Predicting Drug-Induced Liver Injury (DILI) Risk in the Investigational New Drug (IND) Phase of Drug Development

Division of Hepatology and Nutrition (DHN)
Internal review tool

Drug-induced liver injury (DILI) can be a major obstacle to drug approval. Currently, there is no structured assessment process for OND to use when evaluating clinical data for DILI. The Roussel Uclaf Causality Assessment Method (RUCAM) is a scoring system used by several well-known DILI registries. DHN staff wanted to leverage RUCAM to assign objective scores for DILI, however, the tool needed to be validated for use with clinical data submitted in pre-market applications. DHN created an ORISE fellowship to contribute to the development of an algorithm-based scoring tool comparable to RUCAM.

Outcome: In FY21, the fellow contributed to the development and validation of an Access database platform that is fit for this purpose. The new internal review tool, the Patient Level Assessment of DILI (PLAD), will be used by DHN to enhance the DILI Team's accuracy and efficiency by allowing comparison of liver injury cases across marketing applications. Since its development, PLAD has contributed to 24 consults completed by the DILI Team on various new drug applications.

A Look Towards the Future

Our next report will feature fiscal year 2022 (FY22) research outcomes from OND-funded ORISE Fellowships. It will be released in 2024.

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U.S. Food and Drug Administration
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Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993