U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Office of New Drugs Research Outcomes Report

(FY2022-2023)

Table of Contents

Overview 1

Background 1

FY22-23 Research Outcomes 2

External Presentations 2

Peer-Reviewed Publications 5

Regulatory Impacts 7

Future Directions 15

Overview

Laura B. Jaeger, PhD
Associate Director, OND Research Program (OND-RP)

Thank you for your interest in OND's second annual research outcomes report. This report is a celebration of how OND contributed to the field of regulatory science research, which helps the agency to make informed, evidence-based regulatory decisions. The projects featured here are focused on addressing targeted questions that will have an immediate impact on new drug approval decisions, and also provide ample room for the expansion of this research with broad goals that could further increase the impact of the work.

This year, we've identified three broad areas in which we're committed to continuing or expanding our collective effort. As OND's Research Program (OND-RP) moves into our fifth year of working hand-in-hand with OND's scientific review staff, we'd like to encourage you to visit our website for more information on programs that will allow you to collaborate with us directly in the areas listed below.

OND-RP Goals:

- ➔ Continue to promote research that equitably examines all populations using new drugs approved by OND.
- ➔ Continue to develop innovative strategies to efficiently gather or reuse data that addresses information gaps in new drug development.
- ➔ Broaden research to emerging fields like AI, machine learning, and digital health technologies to guide OND reviewers on using these tools for regulatory decision making.

Background

The purpose of this report is to summarize outcomes from OND-funded regulatory science research projects. Outcomes were compiled for fiscal years 2022-2023.

How does OND use regulatory science research 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.

FY22-23 Research Outcomes

External Presentations

In FY22-FY23, **OND delivered 81 research presentations** at external scientific meetings for professional societies. These presentations were significant as they helped OND to collect feedback from external stakeholders on the progress of our research.

Presentation Highlights

Development of a Toolbox of Clinical Outcome Assessments for Assessment of Neuropsychological/Neurodevelopmental and Cognitive Outcomes

Project Lead:
Naomi Knoble, PhD

Affiliation:
Division of Clinical Outcomes Assessment (DCOA)

Presented at:

- **National Organization of Rare Disorders (NORD) Breakthrough Summit 2022, Washington, DC**
- **14th Annual Patient-Reported Outcome Consortium Workshop 2023, Silver Spring, MD**

Measuring clinical trial outcomes for new medical products in rare diseases is a regulatory science challenge. Often there is no regulatory approval precedent and there may be limited knowledge about which aspects of a condition to measure such that fit-for-purpose clinical trial endpoints are not available for most rare diseases. To address this unmet need and advance regulatory science, FDA funded an initiative to establish the Critical Path Institute's Rare Disease Clinical Outcome Assessment Consortium (RD-COAC). The RD-COAC officially launched on January 1, 2022, with the mission to enable pre-competitive, multi-stakeholder collaboration aimed at identifying scientifically sound tools and methodologies for collecting clinically meaningful and patient-centric outcomes data in treatment trials for rare diseases. The RD-COAC has four complementary workstreams to advance measurement science for rare disease clinical trials: (1) Rare Disease COA Resource; (2) Advancing COA Measurement Topic-Focused Working Groups; (3) Rare Disease Discussion Sessions for pre-competitive collaboration and shared learnings; and (4) Dissemination.

The Rare Disease COA Resource, a central pillar of the RD-COAC efforts and its mission to advance measurement science for rare disease clinical trials, was a central goal of FDA's funding initiative. The RD-COAC Resource creates efficiencies for medical product development by freely providing all rare disease stakeholders with information on a published, curated COA library of drug development tools that may apply to a broad range of rare disease drug development programs. While a listing in the Rare Disease COA Resource is not an endorsement that a COA will meet regulatory evidence standards, it is an essential resource for streamlining the identification of COAs that matter to patients in rare disease studies. By including COAs covering common

concepts of interest across many rare diseases, the Rare Disease COA Resource may be used to identify COAs available to measure outcomes of interest in patient registries and natural history studies or in clinical development programs. The inaugural broad domain developed for the Rare Disease COA Resource was “pediatric daily function,” comprising gross and fine motor functioning, self-care, and expressive and receptive communication. Research is already underway for the next measurement topics of pain (e.g., pain severity, pain interference) and sleep (e.g., sleep disturbance, sleep impact), in pediatric non-oncologic populations.

Rare Disease COA Resource:

- https://rdcoas.c-path.org/resource-coas/

Assessment of Physiologically Based Pharmacokinetic Modeling for Predicting Fetal Exposure to Maternal Drugs

Project Lead:
Blessy George, PharmD, PhD

Affiliation:
Division of Pharmacology and Toxicology for Immunology and Inflammation (DPT-II)

Presented At:

- **American Conference on Pharmacometrics (ACOP) 13, Denver, CO**
- **Society of Toxicology Annual Meeting, San Diego, CA**
- **American College of Clinical Pharmacy Annual Meeting, Bethesda, MD**

Medication use is common during pregnancy; however, there is limited information on drug dosing strategies that ensure the safety of the fetus (unborn child) while maintaining efficacy in the pregnant mother. As it is often not feasible to interrupt treatment for serious medical conditions during pregnancy without increasing maternal and fetal risk, there is a need for new non-invasive methods to assess fetal exposure to drugs used by the mother.

The goal of our project is to develop a physiologically based pharmacokinetic (PBPK) model for predicting the extent of fetal exposure to drugs used by the mother. A reliable PBPK model for predicting fetal exposure to medications will facilitate benefit-risk decision-making for the expectant mother as well as inform strategies for prevention or reduction of adverse drug exposures to the unborn child.

Peer-Reviewed Publications

In FY22-FY23, **OND published 94 articles in peer-reviewed journals**. These publications are significant as they provide OND a mechanism for communicating our research fundings with the broader scientific community.

Publication Highlights

Minocycline Pharmacodynamics Against Stenotrophomonas maltophilia in the Neutropenic Murine Infection Model: Implications for Susceptibility Breakpoints

Project Lead:
Thushi Amini, PhD

Affiliation:
Office of Infectious Disease, Immediate Office (OID-IO)

Published in *The Journal of Antimicrobial Chemotherapy*, available at: https://academic.oup.com/jac/article/77/4/1052/6519805

Stenotrophomonas *maltophilia* (*S. maltophilia*) are multidrug resistant gram-negative bacteria that are increasing in prevalence, particularly among critically ill and immunocompromised patients. This pathogen causes severe infections in the respiratory tract, bloodstream, skin and skin structure, and numerous other body sites. Due to biofilm production and antibiotic-resistance mechanisms, there are few antibiotics that retain microbiological activity against *S. maltophilia*, making treatment challenging.

Minocycline displays high susceptibility rates against *S. maltophilia* at the current breakpoint of 4 mg/L. However, no pharmacodynamic data are available to guide dosing or justify this breakpoint.

The murine neutropenic thigh infection model was utilized to determine minocycline pharmacodynamics against four *S. maltophilia* through dose ranging and fractionation studies. The study concluded that the breakpoints for minocycline against *S. maltophilia* needed to be re-assessed as the current dosing regimens may not be efficacious against all isolates defined as susceptible. The results from this study have informed ongoing review of minocycline breakpoints against *S. maltophilia*.

Patient-Reported Outcomes in Pediatric Cancer Registration Trials: a U.S. Food and Drug Administration Perspective

Project Lead:
Vishal Bhatnagar, MD

Affiliation:
Oncology Center of Excellence (OCE)

Published in The Journal of the National Cancer Institute, available at: https://pubmed.ncbi.nlm.nih.gov/33930159/

The 21st Century Cures Act directed the FDA to systematically incorporate patients' experiences, needs, perspectives, and priorities into drug development and evaluation. Patients are experts in their disease because of their lived experience with its symptoms and treatment, and this includes children. In completing patient reported outcomes (PRO), patients can provide unique and valuable information to help inform the FDA's benefit-risk assessment of cancer therapeutics. The collection of PRO data in adult cancer clinical trials has allowed for enhanced assessment of symptoms and function. Emerging evidence also suggests that using PRO assessments to monitor symptoms during routine cancer care can lead to an improvement in clinical outcomes, including survival. Despite these benefits observed in adult patients with cancer, there has been little work done to determine the benefit of collecting PROs in pediatric oncology settings. Studies have demonstrated that clinicians and caregivers frequently under- or overestimate the prevalence, intensity, and burden of symptomatic adverse events compared with children's self-report. Therefore, pediatric PRO data can provide a more comprehensive assessment of the safety and tolerability profile of cancer therapeutics.

The overarching aim of our article was to describe the current status of PROs in pediatric cancer registration trials and provide the FDA's perspectives for future directions to ensure that the Patient-Focused Drug Development (PFDD) initiative benefits patients of all ages. Our review of 17 pediatric oncology trials submitted to the FDA revealed that clinical outcome assessments, and specifically PROs, were rarely collected and applied to pediatric oncology drug development. Our findings highlight that there are opportunities to elicit patient-reported symptom data directly from patients as young as 7 years of age using established pediatric PRO measures in clinical trials.

Regulatory Impacts

In FY22-FY23, **OND's research produced 33 outcomes that directly facilitated regulatory decision making**. OND conducted these studies to address targeted knowledge gaps. The data generated was used to clarify new regulatory pathways. OND's outcomes with the greatest regulatory impact are summarized in the table below.

Outcomes with Regulatory Impact	FY22-23
Informed Drug Development Tools	10
Informed internal policies or regulatory decision making	4
Developed a new assay, technique, or procedure	1
Created a New Review Tool	9
Other Regulatory Tools	5
Sponsor Used Research Results	2
White Paper	1
Regulatory Actions	1

Highlights of Regulatory Impacts

Over the Counter (OTC) Labeling Project (Naloxone)

Project Lead:
Paul Jones, PhD, MA

Affiliation:
Division of Nonprescription Drugs I (DNPD I)

At the request of Congress and other stakeholders, DNPD I responded to the U.S. opioid epidemic with a plan to streamline the regulatory approval process for over-the-counter (OTC) naloxone and, consequently, increase consumer access to life-saving treatment for persons experiencing an opioid overdose. A core element of this plan was to develop a readable, understandable, and actionable model Drug Facts Label (DFL) for OTC naloxone; ensuring DFL consistency and facilitating consumer understanding of key DFL statements for safe and effective use of naloxone.

To support this effort, FDA conducted evidence-based research to create and test a model DFL for OTC naloxone. Subsequently, FDA encouraged industry to pursue development of OTC naloxone using the model DFL as a template for label comprehension studies in support of product labeling.

The impact of this work is far-reaching and evidenced by industry's ongoing use of FDA's model DFL in the development of proposed labeling for OTC naloxone products; increasing consumer access to naloxone through OTC availability and contributing to reduced deaths from opioid overdose.

Impact

- ➔ Findings from this project were published in a *New England Journal of Medicine* article authored by Social Scientist, Barbara R. Cohen, and colleagues (2020) in FDA's Office of New Drugs.
- ➔ Sponsors referenced and used this research in two 2023 NDA submissions: (1) *Narcan (naloxone hydrochloride) nasal spray for OTC*; and (2) *RiVive (naloxone hydrochloride) nasal spray for OTC*, which were approved for nonprescription use.Approved labeling for these OTC Narcan products can be found below:
  - Narcan (naloxone hydrochloride) nasal spray for OTC DFL
  - RiVive (naloxone hydrochloride) nasal spray for OTC DFL

Investigating Sunscreen Drug Product Performance by Measuring Photostability Under Actual Solar Conditions

Project Lead:
Sergio Coelho, PhD

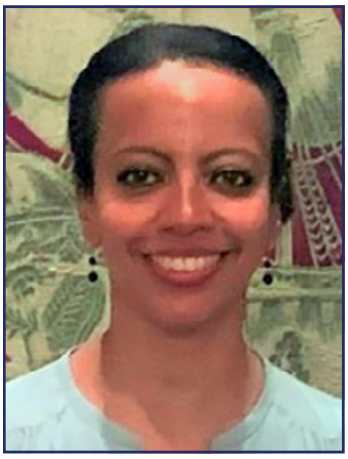
Affiliation:
Division of Nonprescription Drugs II (DNPD II)

Despite widespread knowledge of the adverse effects of sun exposure, skin cancer rates continue to climb. The Surgeon General's Report on Skin Cancer emphasizes that sun protection, including the use of sunscreen, helps prevent the harmful effects of sun exposure, including sunburn, skin cancer, premature skin aging, and eye damage. CDER regulates over-the-counter drugs, including sunscreens, which are the most common sun protection measure. However, sunscreen product performance from exposure to natural sunlight is not fully captured in the SPF or Broad Spectrum tests because they rely on man-made devices designed to simulate the sun (i.e., solar simulators). There is a lack of data on the stability and spectral uniformity of protection of sunscreens under real-world natural sunlight. Our objective was to determine whether potential commercial sunscreen drug products will have quantifiable deficiencies in UV protection efficacy. Our research results underscore how strengthening the broad spectrum criteria as outlined in FDA's 2019 Sunscreen Proposed Rule (and also in the 2021 Sunscreen Proposed Order) may help decrease consumers' overall lifetime UVA burden.

Impact

- ➔ Data generated by this project are currently being used in an ongoing scientific review to inform internal decision making on improving the broad spectrum criteria in the future OTC Sunscreen Final Order.

Use of Quantitative Modeling to Support Pediatric Extrapolation



Project Lead:
Lily Mulugeta, PharmD

Affiliation:
Division of Pediatric and Maternal Health (DPMH)

Several classes of antihypertensive medications are commonly used to treat children with hypertension (HTN), including angiotensin receptor blockers (ARBs). At the initiation of the project, there was only a single ARB approved for use in children 1 to less than 6 years, a stark contrast to the multiple ARBs evaluated and approved for use in adults and older pediatric patients. Requirements for pediatric studies evaluating ARBs in children 1 to less than 6 years of age consisted of: a single-dose PK/tolerability study, a dose-ranging safety and efficacy study, and a 2-year open-label extension. Development programs have faced significant enrollment challenges and delays.

Co-Mentor:
Sudharshan Hariharan, PhD

Co-Mentor:
James Travis, PhD

The aims of our project were: (1) to conduct a systematic review of pediatric hypertension clinical trials for ARBs conducted under PREA and BPCA and submitted to the FDA; (2) Compare dose-response and exposure response relationships and evaluate the potential for using PK data to support extrapolation of efficacy data from pediatric patients 6 to 17 years old to patients 1 to less than 6 years old.

Impact

- ➔ The project found that there were consistent dose-response and exposure-response relationships between pediatric patients 6 to 17 years old and patients 1 to 6 years old.
- ➔ This evidence supported a new regulatory framework for extrapolation of efficacy for angiotensin receptor blockers in patients 1 to less than 6 years of age.

Kidney Transplant Biomarker Qualification:
A Reasonably Likely Surrogate Endpoint for Five-Year Risk of Allograft Loss

Project Lead:
Özlem Belen, MD, MPH

Affiliation:
Division of Rheumatology and Transplant Medicine (DRTM)

There is a critical need to identify an appropriate biomarker for use in kidney transplant clinical trials to develop new immunosuppressant drugs. Our project involves identifying multiple clinical studies (randomized controlled trials conducted in the U.S. and Europe) and available registries (e.g., Scientific Registry of Transplant Patients [SRTR]) from which patient-level data is obtained. The data are then standardized using the Therapeutic Area Data Standards User Guide for Kidney Transplant (TAUG-KT), which was developed through FDA funding by the Coalition for Accelerating Standards and Therapies (CFAST), CDISC, C-Path, ASN, KHI and AST. Finally, the resulting data repository is analyzed and validated to identify predictors of long-term outcomes in kidney transplant patients.

Impact

- The results of this project were presented at a public workshop titled “Accelerating Medical Product Development in Kidney Transplantation Through a Public-Private Partnership” held on September 22, 2022. The workshop focused on: (1) qualifying a composite surrogate for long-term graft loss after kidney transplantation; (2) real-world evidence use in transplant clinical trials; and (3) potential future endpoints in kidney transplantation.
- This project has resulted in a biomarker qualification submission. Transplant Therapeutics Consortium (TTC) and C-PATH proposed qualification of a reasonably likely surrogate endpoint biomarker to predict five-year risk of allograft loss in kidney transplant recipients. The qualification plan has been accepted by the CDER Biomarker Qualification Program (BQP) and is currently under review by the FDA.

Pregnancy and Lactation Labeling Rule (PLLR):
Health Care Provider Testing to Improve Health Communications Related to Lactation

Project Lead:
Miriam Dinatale, DO, FAAFP

Affiliation:
Division of Pediatrics and Maternal Health (DPMH)

Most breastfeeding individuals take at least one prescription drug, yet limited data are available to inform the safety of these drugs during breastfeeding. To improve risk communication, the FDA implemented the Pregnancy and Lactation Labeling Rule (PLLR) in 2015, which added a narrative summary of available risk information related to pregnancy and lactation for prescription drug labeling. Studies on PLLR labeling revealed that although healthcare providers (HCP) found these details valuable, the narrative was regarded as too long to support decision-making during patient encounters. The objective of our project was to identify gaps in HCP understanding of the PLLR and to assess the utility of adding a concise summary to the Lactation subsection (8.2) of the labeling to complement the narrative and succinctly communicate to busy HCPs a prescription drug's risk when used during lactation.

Twenty-five online focus groups were conducted with HCPs to obtain feedback on the proposed concise summary and discuss their prescribing/counseling decisions for four fictitious prescription drugs including one vaccine. We found that HCPs utilized the concise summary to make initial prescribing/counseling decisions and used the details from the prescribing information narrative to make a more comprehensive benefit-risk assessment. These findings indicate a need to continue to improve communication about available prescription drug safety data for breastfeeding individuals, educate HCPs about prescription drug labeling content limitations, and conduct clinical lactation studies to provide sound data to inform evidence-based decision making about benefit-risk of drug use during lactation.

Impact

- ➔ The safety findings resulted in two public workshops.
  - The first workshop "Pregnancy and Lactation Medication Information for the Healthcare Provider" was held on May 11, 2022. The presentation, which involved a collaboration between FDA's Office of Women's Health (OWH) and the Division of Pediatrics and Maternal Health (DPMH), discussed the Pregnancy and Lactation Labeling Rule (PLLR) and helped healthcare providers examine how prescription drug labeling can be used to inform prescribing for pregnant and lactating individuals.
  - The second workshop titled "Engaging Providers to Address Knowledge Gaps on Medication Use in Pregnancy and Lactation" was held on October 27, 2022. The presentation provided an overview of the studies enrolling pregnant and lactating individuals and provided information on how health care providers can become involved in advancing research in pregnant and lactating individuals.
- ➔ The findings of this study were published in Research in Social and Administrative Pharmacy, which is available at this link

Assessment of the Efficacy of Acute Pain Treatments

Project Lead:
Allison Meyer, BS

Affiliation:
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

With the advent of the opioid epidemic and the implication that the over treatment of acute pain with opioids are a contributing component to abuse, there is a strong interest in the identification of new approaches to acute pain care that will minimize the amount of opioid used while maintaining adequate control of acute pain. This will require a better understanding of the level of efficacy of other therapies, and ideally, the development of prediction models for patients to identify those most likely to respond to those therapies. To date, no studies have been conducted using patient-level data to define the level of response and predictors of response to specific therapies across a range of conditions, making our study particularly relevant to the improvement and refinement of patient care and to provide better evidence for the use of different types of analgesic therapies, which will allow a reduction in the need for pure opioid agonists to achieve adequate pain control. Advances in data storage and computing provide the opportunity for the harmonization of electronic data sets and completion of complex analytic modelling, allowing us to develop rate of response and prediction models to support or refute the potential usefulness of different analgesic treatments for acute pain. The aim of our study is to provide vital information needed to inform the ongoing discussion about the appropriate use of both opioid and non-opioid analgesics in acute pain care and how FDA should approach the regulation of their relative efficacy and safety.

Impact

- ➔ This project resulted in the development of an overall analysis system, “TidyPain”, which provides a standardized process for uploading harmonized data from individual studies into a common analytic data set, as well as a systematic approach to overall analyses.

MIDD in the Evaluation and Development of Neurological Drug Products

Project Lead:
Kevin Krudys, PhD

Affiliation:
Office of Neuroscience, Immediate Office (ON-IO)

Despite significant and sustained investments in drug development in neurological diseases, bringing transformative therapies to patients in need remains challenging and would be aided by designing optimal trials to determine efficacy and safety. Trial design challenges include, but are not limited to, incomplete understanding of underlying disease progression and relevant sources of variability, inefficiencies and/or limitations in traditional clinical trial designs and analysis methods, and inadequate trial size and duration. These issues increase the risk for sponsors to engage in late-stage drug development and impede development of novel therapies.

Through feedback and collaboration with the FDA, C-Path has developed model-informed dug development (MIDD) tools designed to address unmet needs in designing trials for Alzheimer's disease (AD), Parkinson's disease (PD), Duchenne muscular dystrophy (DMD), and more. MIDD tools are vital because they help synthesize current knowledge about disease progression and sources of variability, incorporate sophisticated trial design methods, and help inform adequate trial size and duration through clinical trial simulation (CTS) and sample size/effect size estimation. Building on previous work under C-Path in developing MIDD tools to advance clinical trials for neurologic disease, and through funding from a broad agency announcement, CDER and C-Path have collaborated to add new tools and capabilities that are implemented as user-friendly graphical user interfaces via the R Shiny web app.

Impact

➔ This project has resulted in several drug development tools:

- Alzheimer's disease CTS tool with COVID-19 module: https://cpath.shinyapps.io/BAA_Covid/
- Parkinson's disease CTS tool with platform trial module: https://cpath.shinyapps.io/cts-platform-trials/
- Parkinson's disease CTS tool with randomized delayed start module: https://cpath.shinyapps.io/PD_CTS_with_RDS_v3/
- Duchenne's muscular dystrophy CTS tool with treatment switching module: https://cpath.shinyapps.io/DMD_CTS_with_Treatment_Switching_v1

Future Directions

Next year's report will feature research outcomes from fiscal year 2024 (FY24).
In the meantime, if you would like to contribute your suggestions for addressing new knowledge gaps in regulatory research, you may contact the OND-RP by e-mail at ONDResearch@fda.hhs.gov.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Food and Drug Administration
www.fda.gov

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