U.S. FOOD & DRUG ADMINISTRATION

OFFICE OF CLINICAL PHARMACOLOGY

OFFICE OF TRANSLATIONAL SCIENCES

2023 Annual Report

Amplifying Patient Voices Through Science and Innovation

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Director's Message

Issam Zineh
PharmD, MPH, FCP, FCCP
Director - Office of Clinical Pharmacology

The past several years have highlighted the importance of multidisciplinary science, community engagement, and a solutions-oriented mindset from the public health perspective. The challenges, successes, and failures of this seminal period, hallmarked by the transformative nature of the COVID-19 pandemic, reinforced our Office's commitment to strengthening partnerships, sharing experiences and knowledge, and continuing to make patients the center of our daily work.

Our stakeholders are numerous and diverse, including patients, advocates, drug developers, international regulators, scientists, and health care providers (HCPs). This richness drives our mission and vision. In this Annual Report, we share how staff at the U.S. Food and Drug Administration's (FDA's) Office of Clinical Pharmacology (OCP) translate their expertise into their work, with the ultimate goal of accelerating science and the delivery of safe and effective drugs to the public.

In 2023, OCP advanced several innovative scientific and regulatory programs. One of our flagship efforts, the Model-Informed Drug Development (MIDD) Paired Meeting Program, continues to advance quantitative medicine approaches in the development and regulatory assessment of novel therapeutics. These approaches have accelerated drug development in several ways, including confirming the utility of novel biomarkers, refining dosing, improving safety, and validating efficacy for patients. Other programs on real-world evidence, treatments for rare diseases, and artificial intelligence have made significant strides as we continue to engage within the FDA and with the scientific, regulatory, and patient communities.

In OCP, patient-centered engagement is a core value and is reflected in our strategic plan and priorites. The development of this plan was community- and data-driven, ensuring that our strategic plan is timely and relevant. As we moved into the implementation phase in 2023, OCP staff leveraged the skills and input from a broad set of collaborators whenever possible, understanding that this knowledge will help us accelerate the science of clinical pharmacology and translational medicine and advance public health. In addition, our annual research showcase, OCP Day 2023, featured keynote and panel discussions from several patient advocates, who shared their invaluable experiences navigating treatment for their diseases. Hearing from patients directly is critical to our work, and we look forward to continuing that relationship across a broad range of patient groups.

It is an exciting time to maximize our engagements, capitalize on our diverse experiences, and create more integrative touch points to advance our public health. OCP's passionate commitment to excellence cannot be overstated, and our eagerness to share, learn, and collaborate is unbounded. Because of our dedicated staff, the future of clinical pharmacology as a translational science that advances therapeutics for the benefit of patients is bright.

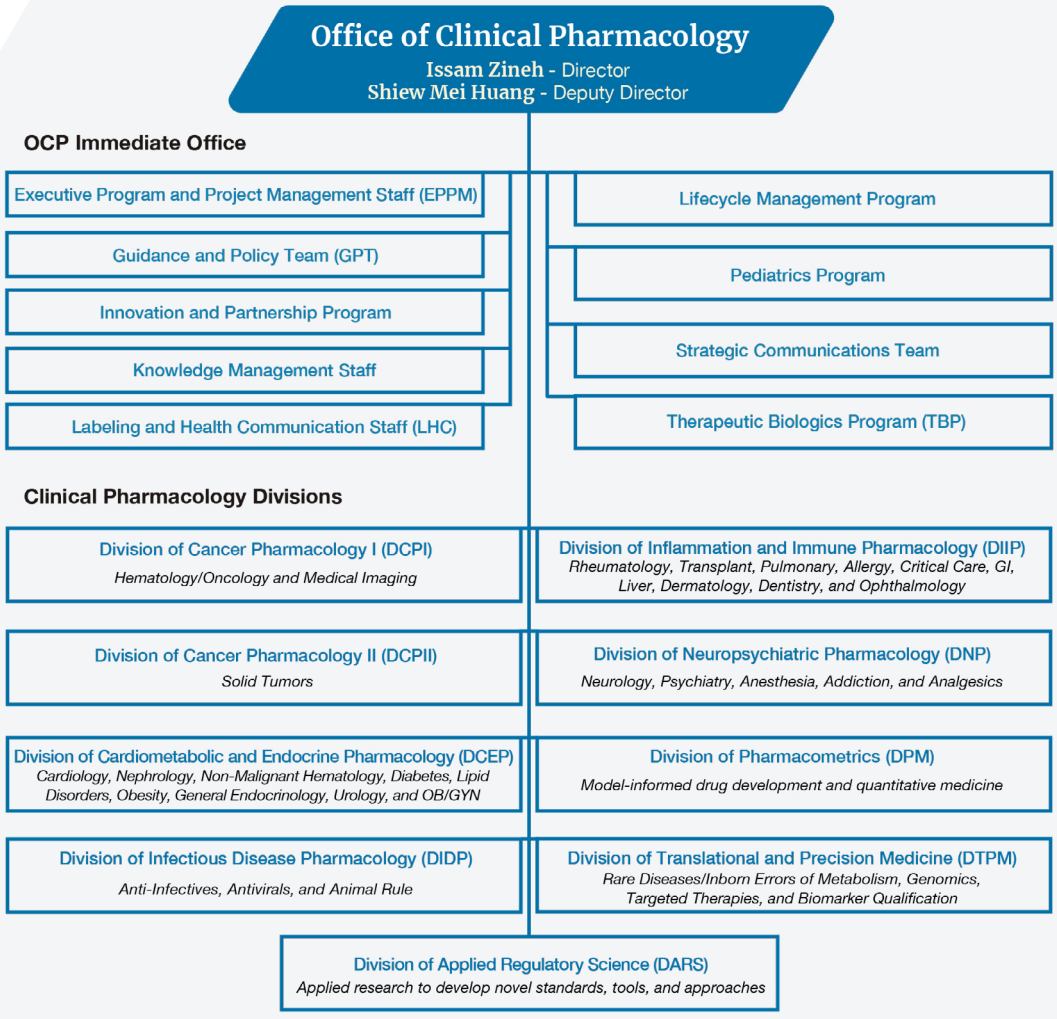
OUR VISION

Improve public health by building and translating knowledge of drug-response into patient-centered regulatory decisions of the highest quality

Organization

OCP is a patient-focused, collaborative, and highly multidisciplinary organization dedicated to applying clinical pharmacology principles and approaches to promote and protect global public health. OCP, an office within the FDA's Center for Drug Evaluation and Research (CDER) Office of Translational Sciences (OTS) super-office, is comprised of over 270 pharmacologists, pharmacists, biologists, chemists, physicians, nurses, project and program managers, and administrative professionals (See Figure 1). While our expertise is diverse, we are united in our core values - stewardship, leadership, excellence, connectedness, diversity and respect – that empower our staff to translate knowledge into patient-centered scientific advances and regulatory decisions. Our strategic priorities reinforce our commitment to patients, innovation, and our people (See Figure 2).

Figure 1. **OCP Organizational Structure**



OUR MISSION

- Advance the development of innovative new medicines by applying state-of-the-art scientific principles
- Promote therapeutic optimization and individualization through best practices in research, policy development, and drug evaluation throughout the product lifecycle

Figure 2.

OCP Strategic Priorities

ADVANCE OUR SCIENCE FOR THE BENEFIT OF PATIENTS

- Foster the development and application of innovative scientific approaches to enhance drug development and regulatory decisions
- Optimize patient outcomes through individualized pharmacotherapy
- Enhance the OCP interdisciplinary review process to elevate our science

BOLSTER PATIENT-CENTERED ENGAGEMENT

- Engage with patients, caregivers, and HCPs to better understand their pharmacotherapeutic needs
- Provide patient-centric recommendations in reviews and labeling
- Promote how clinical pharmacology and OCP advance therapeutic optimization and individualization of drug products

ELEVATE OUR PEOPLE

- Provide staff development and leadership opportunities for all career stages
- Cultivate a culture of meaningful recognition
- Ensure OCP has a welcoming and transparent environment that fosters well-being and belonging

$$C = C_0 \cdot e^{-ke \cdot t}$$

$$C = a \cdot e^{-\alpha t} + b \cdot e^{-\beta t}$$

$$t_{1/2} = \frac{0.693 \cdot Vd}{CL} = \frac{\ln(2)}{k_e} = \frac{0.693}{k_e}$$

$$Q_h + f'_{u,b} \times (PS'_{in,inf} + CL_{pd,inf})$$

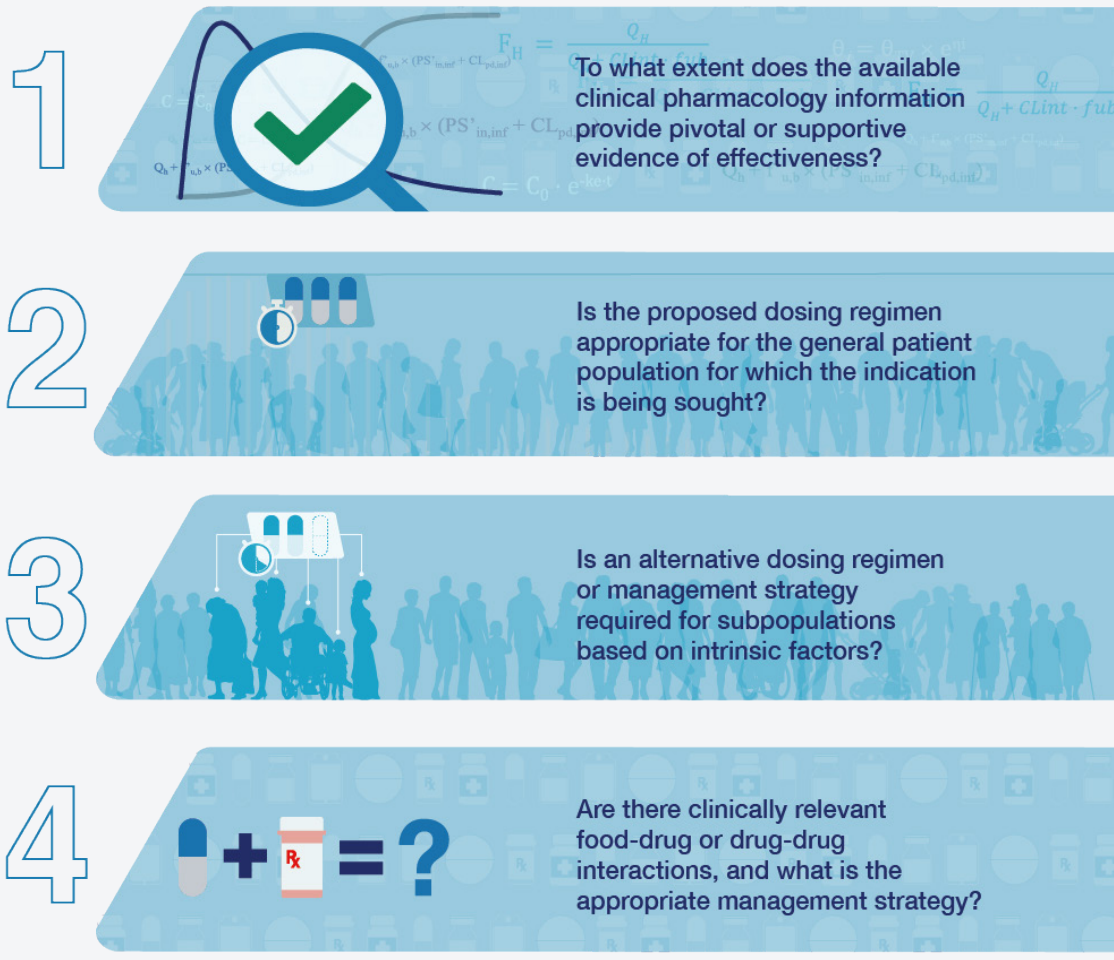
$$\sum_{i=1}^{n} (f_{m,i} \times CL_{int,met}) \cdot fub$$

$$F_H = \frac{Q_H}{Q_H + CLint \cdot fub}$$

Regulatory Drug Evaluation

OCP's regulatory evaluation process ensures that approved drugs and biologics are administered at the right doses to the right patients at the right time in their disease process. To achieve this goal, OCP uses a patient-centric, issue-based strategy to guide the evaluation of drug applications and incorporate the views of the multidisciplinary clinical pharmacology team (bioanalytical method validation, drug disposition, pharmacology and biomarkers, quantitative methods, drug safety, pharmacotherapy, and clinical trial methods) (See Figure 3). In 2023, we conducted over 5600 reviews of investigational new drug (IND) submissions to facilitate drug development. Our review findings for new drug applications (NDAs), NDA supplements, and biologics license applications (BLAs), including 351(k) applications (i.e., biosimilars), were integrated into benefit/risk assessments, ultimately bringing 55 safe and effective new drugs and biological products to patients in 2023 (See Table 1).

Figure 3. **OCP's Issue-Based Approach to Drug Evaluation**



Innovative Regulatory Approaches in OCP Review

Guided by this issue-based strategy, OCP staff gather all evidence from the appropriate clinical pharmacology disciplines to inform regulatory decisions (e.g., approvability, labeling, post-approval requirements, and product lifecycle management). Our staff assess clinical pharmacology information in applicant submissions, integrating these data with certain previously established knowledge to address issues of dose selection and optimization, therapeutic individualization, and benefit/risk balance. Informed by current science and policy, our assessments (reviews) identify any critical gaps in the understanding of conditions for optimal therapeutic use, and we recommend studies or leverage wide-ranging scientific approaches that can practically address these knowledge gaps. As you will see in the following pages, OCP uses state-of-the-art approaches to maximize the utility, safety, and efficacy of drug products, both for the general patient population and patients with specific considerations (e.g., patients with renal or hepatic impairment, young children or neonates, patient subsets with specific genetic mutations). In some cases, these approaches have allowed the regulatory approval of drugs for patients not specifically studied in clinical trials, accelerating the delivery of innovative medicines to patients who otherwise would not have been part of the indicated patient population.

OCP Review At-a-Glance

Investigational New Drug Reviews Conducted in 2023

Over 5600

Drug Development Meetings in 2023

Over 3200

New Molecular Entities and New Therapeutic Biological Products Approved in 2023

55

Our Office integrates state-of-the-art science with innovative regulatory programs to enhance drug development and regulatory evaluation. OCP leads the highly impactful MIDD Paired Meeting Program to accelerate and optimize drug development by providing an opportunity for sponsors and the FDA to discuss MIDD approaches within a specific drug development program. In addition, OCP staff are leaders in other regulatory programs that use the latest advances in clinical pharmacology to accelerate drug development, such as CDER's Accelerating Rare Disease Cures Program, which aims to accelerate the development of effective and safe treatment options for patients with rare diseases. OCP plays a critical role in the regulatory qualification of Drug Development Tools (DDT) through the FDA's Fit-for-Purpose (FFP) Initiative, focusing on methods and models for dose-finding and clinical trial design.

Table 1.

OCP Contributions to Novel Drug and Biologic Approvals

Therapeutic Area	Drug Name	Primary Review Contribution				
		Assessed pharmacodynamic/ biomarker data as primary or supportive evidence of effectiveness	Mitigated risk	Evaluated/proposed extrapolation or bridging strategies	Optimized dosing regimen	Minimal (not systemically administered)
Cardiology/ Hematology/ Nephrology	Aphexda		●		●	
	Fabhalta		●		●	
	Filspari	●	●		●	
	Inpefa		●		●	
	Jesduvroq		●		●	
	Ojjaara		●		●	
	Rivfloza	●	●	●	●	
	Ryzneuta		●		●	
Infectious Disease	Beyfortus		●	●	●	
	Defencath					●
	Paxlovid		●	●	●	
	Rezzayo		●		●	
	Xacduro	●	●		●	
Inflammation/ Immunology/ Dermatology	Bimzelx		●		●	
	Filsuvez					●
	Joenja		●		●	
	Litfulo		●		●	
	Omvoh		●		●	
	Velsipity		●		●	
	Veopoz	●	●	●	●	
Medical Imaging	Posluma				●	
Metabolic/ Endocrine	Brenzavvy		●		●	
	Ngenla		●		●	
	Sohonos		●		●	
	Veozah		●		●	
Neurology/ Psychiatry	Agamree		●	●	●	
	Daybue		●	●	●	
	Exxua		●		●	
	Leqembi	●	●		●	
	Qalsody	●	●		●	
	Rystiggo		●	●	●	
	Skyclarys	●	●		●	
	Wainua	●	●		●	
	Zavzpret		●		●	
	Zilbrysq	●	●	●	●	
	Zurzuvae		●		●	
Oncology	Augtyro		●		●	
	Columvi		●		●	
	Elrexfio		●		●	
	Epkinly		●		●	
	Fruzaqla		●		●	
	Jaypirca		●		●	
	Loqtorzi		●		●	
	Ogsiveo		●		●	
	Orserdu		●		●	
	Talvey		●		●	
	Truqap		●		●	
	Vanflyta		●		●	
	Zynyz		●		●	
Ophthalmology	Izervay					●
	Miebo					●
	Xdemvy					●
Rare Disease	Elfabrio	●	●		●	
	Lamzede	●	●	●	●	
	Pombiliti		●		●	

Demystifying Quantitative Approaches in Clinical Pharmacology Review

The term MIDD refers to the use of exposure-based, biological, and statistical models to preclinical and clinical data to facilitate decision-making in drug development and regulatory evaluation. This year, we have also adopted the term 'quantitative medicine' to better acknowledge the potential impact of these approaches on a given patient. Quantitative medicine utilizes all available data sources (e.g., clinical trial data, pharmacology, biology, real-world evidence) and technical tools to optimize the benefit-risk profile of a new drug, improve a dosing regimen for safety, efficacy, and tolerability, increase access to patients who might not have been well represented in clinical trials, and more. Below, we describe some of the technical approaches commonly used in quantitative medicine and how they were used to bring new therapies to patients in 2023.

> *"With exciting innovations on the horizon, quantitative medicine stands poised to unlock transformative solutions for drug development. We are excited to champion, advance, and integrate quantitative medicine for patient and societal benefit."*
>
> **Rajanikanth Madabushi, PhD**
>
> Associate Director for Guidance and Scientific Policy

POPULATION PHARMACOKINETICS

Individuals taking the same dosing regimen can have clinically relevant differences in drug concentrations that require a change in dose or dosing regimen. These differences in drug concentrations can be attributed to intrinsic patient factors, such as differences in body weight, presence and extent of hepatic or renal impairment, or to extrinsic factors, such as food or concomitant medications.

Population pharmacokinetic (population PK) analysis is a well-established, quantitative method that can characterize some of the variability in drug concentrations among individuals by determining factors that affect drug exposure. These analyses can then inform strategies to select initial dosage regimens, manage dosing and administration for a given subpopulation, plan subsequent studies, or support labeling (FDA final guidance Population Pharmacokinetics). In 2023, population PK analysis was used during the review of the majority of new drugs approved. This quantitative method facilitated dosing regimen optimization based on food intake, body weight, and presence of renal or hepatic impairment. It was used to determine alternate dosing schedules to manage missed doses/dose interruptions, assess the relationship between exposures and pharmacodynamic (PD) markers, and develop dosing regimens for children when not studied in clinical trials.

EXPOSURE-RESPONSE ANALYSES

Understanding the relationship of a drug's dose/concentration in the body and the benefits and risks of a drug is a critical component of the clinical pharmacology review. Information on exposure-response relationships for favorable and unfavorable effects can help inform if and how exposure can be adjusted for various subsets of the patient population through alternate dosing recommendations (FDA final guidance Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications). OCP staff conducted exposure-response analyses for the vast majority of new drugs approved in 2023 and had a significant impact on identifying and characterizing the relationships between exposure and a broad range of endpoints or biomarkers, such as mechanistic effects, potential or accepted surrogates, and clinical effects related to efficacy and safety. When clinical data were difficult to obtain (e.g., in diseases with variable natural histories or in ultra-rare genetic diseases), OCP staff were instrumental in assessing PD endpoints to inform benefit/risk assessments and reduce uncertainty in regulatory decision-making.

PHYSIOLOGICALLY BASED PHARMACOKINETIC ANALYSES

A physiologically based pharmacokinetic (PBPK) analysis combines physiology, population, and drug characteristics to model and simulate the PK and/or PD behaviors of a drug. PBPK model predictions can be used to support decisions on whether, when, and how to conduct certain clinical pharmacology studies and to support dosing recommendations in product labeling (FDA final guidance Physiologically Based Pharmacokinetic Analyses — Format and Content). OCP staff reviewed PBPK models for new drugs approved in 2023, largely to determine the extent and severity of drug interactions, but also to determine dosage adjustments for patients not studied in clinical trials (e.g., patients with severe hepatic impairment) and how best to manage missed doses.

QUANTITATIVE SYSTEMS PHARMACOLOGY

Quantitative systems pharmacology (QSP) mechanistically and quantitatively integrates biological, drug, and clinical trial information to model and simulate drug responses and variability in patients' responses to inform drug development decisions. OCP staff played a key role in reviewing QSP models, gaining critical information on dosing in patients who were unable to be studied in clinical trials and the safest way to address missed doses. In May 2023, OCP and the University of Maryland Center for Regulatory Science and Innovation (MCERSI) held a workshop on the use of QSP approaches in rare disease drug development (See also the Communication, Outreach, and Engagement section of this report for more information). Regulators and scientists discussed the challenges of drug development for rare diseases, including the small number of patients available for clinical trials and a lack of well-characterized biomarkers, and provided examples of how QSP models can help understand inter-individual variations in the course of disease and a drug's safety and efficacy.

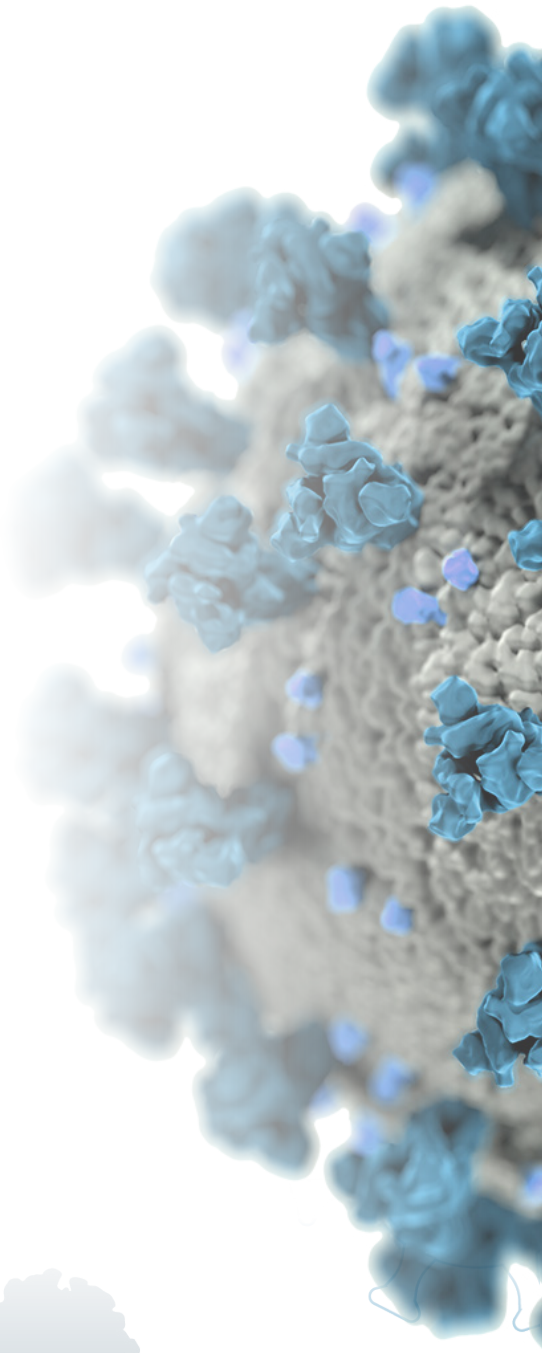
SPOTLIGHT

Using Quantitative Approaches to Optimize a Drug's Utility During Public Health Crises – COVID-19

Since the COVID-19 National Public Health Emergency was declared in 2020, OCP continues to ensure the availability of treatments for patients fighting the devastating effects of this disease in an ever-changing SARS-CoV-2 variant landscape. OCP staff were instrumental in the 2023 full approval of Paxlovid (nirmatrelvir/ritonavir) for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. It is the first oral antiviral treatment for COVID-19 in adults.

The clinical pharmacology review of Paxlovid highlights the use and impact of quantitative approaches in maximizing the safety and utility of this drug. For example, understanding the exposure-response relationships for efficacy and safety helped OCP review staff lay the foundation for potential dosage adjustments for specific populations. Population PK analyses were used to determine covariates that affected exposure levels, resulting in dosage adjustments or recommendations to avoid use for certain patients with renal or hepatic impairment.

PBPK analyses were used to assess the drug-drug interaction (DDI) potential of Paxlovid, as some DDIs could result in greater exposures of certain concomitant medications, leading to potentially severe, life-threatening, or fatal events, while other DDIs could cause a potential loss of virologic response and possible resistance. OCP staff also determined the appropriateness of a QSP model to help determine dosing in immunocompromised patients. Lastly, because Paxlovid was extensively used under an Emergency Use Authorization (EUA), OCP staff were able to assess real-world evidence in determining the drug's safety and effectiveness. In sum, quantitative medicine approaches used by OCP review staff were effective in improving the safety and extending the utility of this life-saving drug.



Policy

OCP published a total of 9 guidances and policies in 2023, providing recommendations on a range of clinical pharmacology topics, including drug interactions, model-informed drug development, submitting pharmacogenetic data to the FDA, clinical pharmacology studies for peptide therapeutics, bioequivalence studies, optimizing drug dosing for oncology drugs, and prioritization and review processes for INDs (See Figure 4). OCP staff played lead roles in policy harmonization on an international scale. One guidance was published in 2023 under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which further helps to streamline global drug development through recommendations that are acceptable to regulatory agencies worldwide. OCP representatives are also leaders in working groups for ICH M12 – Drug Interactions and ICH M15 – General Considerations for Model-Informed Drug Development.

Figure 4. **OCP Guidances Published in 2023**

CLINICAL PHARMACOLOGY REVIEW

OCP Prioritization, Triage, and Review Process for INDs and Pre-INDs (MAPP)

DOSE OPTIMIZATION

Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases (Draft guidance)

DRUG INTERACTION

Clinical Drug Interaction Studies With Combined Oral Contraceptives (Final guidance)

Drug-Drug Interaction Assessment for Therapeutic Proteins (Final guidance)

Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications (Final guidance)

PHARMACOGENOMICS

Pharmacogenomic Data Submissions (Draft guidance)

PHARMACOKINETICS

M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (Draft guidance)*

QUANTITATIVE MEDICINE

Prescription Drug User Fee Act of 2023 VII Meetings Program for Model-Informed Drug Development Approaches (Federal Register Notice)

SPECIFIC DRUG PRODUCT DEVELOPMENT

Clinical Pharmacology Considerations for Peptide Drug Products (Draft guidance)

**This guidance was developed under the auspices of ICH.*

OCP Research At-a-Glance

Research Projects

122

Research Budget (Approximate)

$19.0M

Research Fellows

43

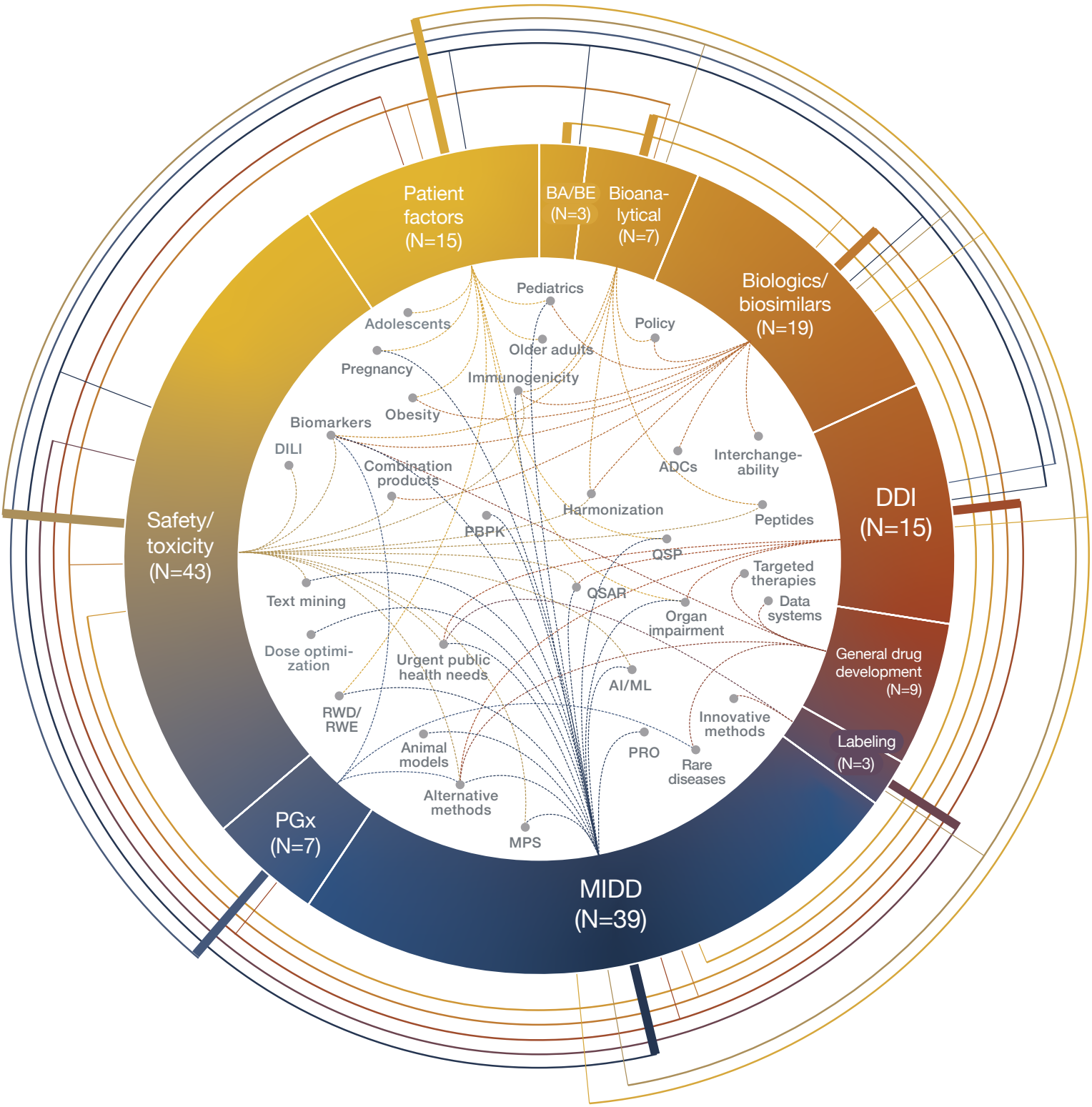
Regulatory Science Research

The foundation of sound regulatory decision-making is robust, innovative science. The OCP regulatory science research program addresses regulatory challenges by applying the science of clinical pharmacology and translational medicine to ensure the quality, efficacy, and safety of drug and biologic products used by patients and consumers. We use pioneering analytical methods, models, and tools to answer complex regulatory questions, inform use of new medicines, and address urgent public health needs.

Our research portfolio in 2023 was multidimensional and collaborative and consisted of 122 projects using a variety of laboratory, computational, and translational methods to address regulatory challenges across a range of therapeutic areas (See Figure 5). Our staff conducted quantitative structure, molecular and mechanistic modeling, toxico-surveillance, and clinical studies to address urgent public health issues such as the opioids crisis, nitrosamine impurities in medications, sunscreen safety, and COVID-19. Research efforts in bioanalytical methodologies, large molecules, and cardiac safety informed policy and facilitated global regulatory harmonization. The potential of artificial intelligence/machine learning data analysis automation systems and text mining to improve adverse event assessment and molecular target identification was explored, and research in the areas of transporter-based drug interactions, immunogenicity, biomarkers, and organ impairment led to an improved understanding and assessment of risk.

In 2023, FDA partnered on projects through FDA's collaborative mechanisms and agreements to address critical public health needs, such as dose optimization for understudied populations, supporting efficacy for rare disease treatments, characterizing abuse potential for opioid and opioid-like compounds, and advancing women's health. Research collaborations advanced state-of-the-art methodologies and their application to drug development, including alternatives to animal testing (e.g., in vitro models, microphysiological systems, the Comprehensive In Vitro Proarrhythmic Assay (CIPA)). OCP published research outcomes in 149 publications in peer-reviewed journals, highlighting collaborations with stakeholders in the clinical pharmacology community and beyond for the purpose of advancing our science for the benefit of patients (See Figure 6 and Appendix). OCP's regulatory research activities are further enhanced by our robust research fellowship program which offered unique development opportunities to 43 scientists in 2023.

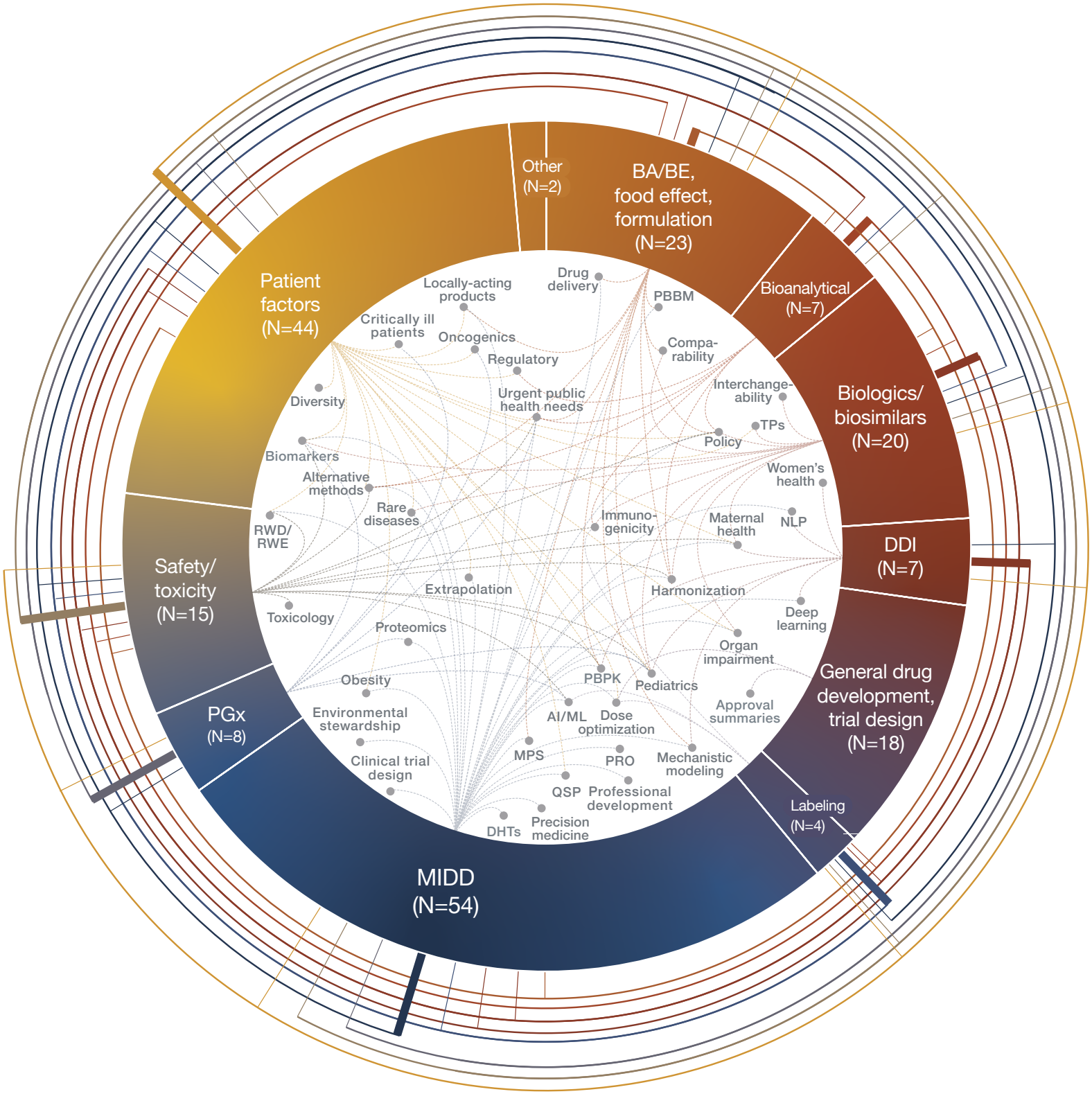
Figure 5. **OCP Research Focus Areas in 2023**



Numbers represent total counts by focus area. A research project may cover multiple focus areas; these relationships are represented by bold color lines. Dotted lines represent the various sub-topics in those areas. ADCs: antibody-drug conjugates; AI/ML: artificial intelligence/machine learning; BA/BE: bioavailability/bioequivalence; DDI: drug-drug interaction; DILI: drug-induced liver injury; MIDD: model-informed drug development; MPS: microphysiological systems; PBPK: physiologically based pharmacokinetics; PGx: pharmacogenomics; PRO: patient-reported outcomes; QSP: quantitative systems pharmacology; QSAR: quantitative structure-activity relationship; RWD/RWE: real-world data/ real-world evidence.

Figure 6.

OCP Publication Focus Areas in 2023



Numbers represent total counts by focus area. A publication may cover multiple focus areas; these relationships are represented by bold color lines. Dotted lines represent the various sub-topics in those areas. AI/ML: artificial intelligence/machine learning; BA/BE: bioavailability/bioequivalence; DDI: drug-drug interaction; DHTs: digital health technologies; MIDD: model-informed drug development; MPS: microphysiological systems; NLP: natural language processing; PBBM: physiologically based biopharmaceutics modeling; PBPK: physiologically based pharmacokinetics; PGx: pharmacogenomics; PRO: patient-reported outcomes; QSP: quantitative systems pharmacology; RWD/RWE: real-world data/real-world evidence; TPs: therapeutic proteins.

SPOTLIGHT

OCP Research Promotes Women's Health

OCP advances the science of women's health by applying clinical pharmacology principles and innovative model-informed methods to optimize therapies for women. We further understanding of sex differences in pharmacokinetics and pharmacodynamics, as well as differences during pregnancy, to inform dosing and benefit/risk assessment for new and approved drugs. In 2023, OCP partnered with the Bill and Melinda Gates Foundation through a Cooperative Research and Development Agreement to examine the feasibility of an exposure-based paradigm aimed at streamlining the development and approval pathways of long-acting contraceptives. This partnership aims to support development of future innovative contraceptive technologies with novel mechanisms of delivery and improve benefit/risk assessment of contraceptive products. In addition, our research partnership with MCERSI is exploring a PBPK model-informed framework to prioritize drugs to be studied during pregnancy. Through use of a web-based tool for research population cohort and feasibility queries, investigators are establishing a database query protocol to gather information on the most commonly prescribed drugs for pregnant women in the US from electronic health records. In addition to these collaborative projects, OCP scientists utilized quantitative and mechanistic modeling approaches to characterize physiologic changes during pregnancy and the potential effect of those changes on efficacy and safety of antimalarials drugs, develop a mechanistic PK/PD model for parasitic load, and optimize dosing strategies for antiparasitic therapies. Collectively, these research efforts enhance understanding of the factors that influence drug exposure and response in women and improve the health of women worldwide.

> *"Addressing women's health issues leads to improved maternal and child health, reduced mortality rates, and increased quality of life, creating a positive ripple effect around the world. We are proud to play a role in advancing women's health."*
>
> **Shirley Seo, PhD**
>
> Director - Division of Cardiometabolic and Endocrine Pharmacology

OCP Division of Applied Regulatory Science

OCP's dedicated research division, the Division of Applied Regulatory Science (DARS), moves new science into the drug review process and addresses emergent regulatory and public health questions for the Agency. DARS forms multidisciplinary teams to conduct mission-critical research and provide answers to scientific questions and solutions to regulatory challenges. Staffed by experts across the translational research spectrum, DARS scientists frequently engage stakeholders on projects, including leading academic, government, and private institutions, to tackle some of the most complex challenges facing FDA. DARS capabilities include laboratory-based research specializing in omics, bioanalysis, microphysiological and cellular systems, immunology, and electrophysiology as well as in silico research performed by informatics and computational modeling groups.

> *"Our goal is to move new science into the drug review process and close the gap between scientific innovation and drug review. We're not just doing discovery basic science, but we're trying to take those new scientific discoveries and change how we review new drugs."*
>
> **David Strauss, MD, PhD**
>
> Director - Division of Applied Regulatory Science

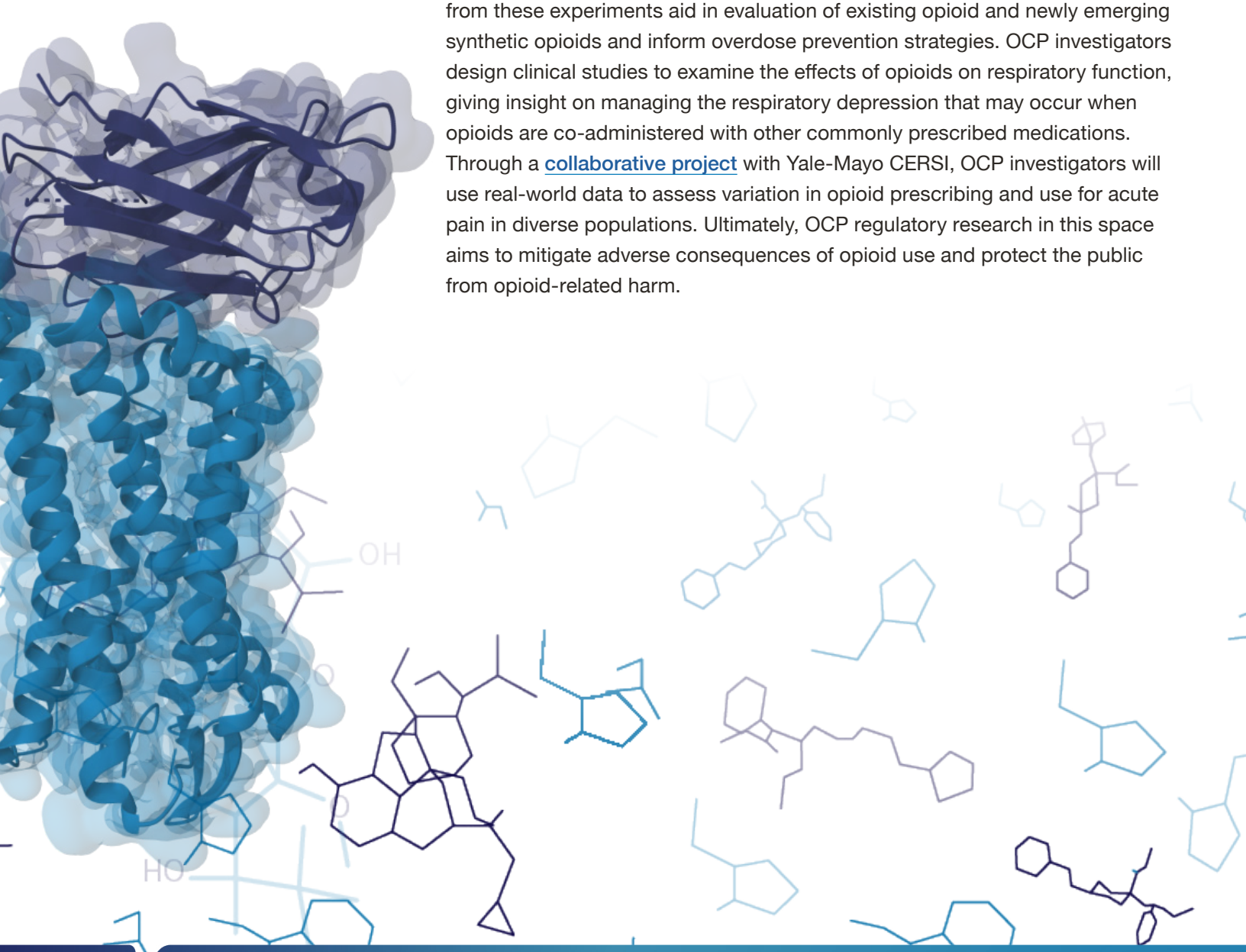
In addition, DARS conducts clinical research focused on facilitating new and follow-on product development and assessing the safety of marketed drugs. Using applied research, DARS investigates questions related to clinical pharmacology, medical toxicology, systems pharmacology, chemistry, and biology. Regulatory areas of research focus in DARS include assessing the systemic absorption of sunscreens, evaluating whether certain drugs convert to carcinogens in people, studying drug interactions with opioids, optimizing opioid antagonist dosing in community settings, removing barriers to biosimilar and generic drug development, and advancing therapeutic development for rare diseases. DARS is tasked with wide-ranging issues that encompass regulatory science, and in turn helps the Agency solve these challenges.

For more details on our dedicated research division, visit the DARS website.

Research Impacting Patients in 2023

COMBATING EMERGENT PUBLIC HEALTH CRISES – OPIOIDS

One of the highest priorities of the FDA is advancing efforts to address the crisis of misuse and abuse of opioid drugs harming patients and families. Opioid overdoses, for example, are claiming lives at a staggering rate. OCP is responding to this crisis by applying innovative PD modeling and simulation systems and well-designed clinical research studies to expand our understanding of opioids and opioid-like compounds. OCP scientists use novel structure-based computational tools such as the Public Health Assessment via Structural Evaluation (PHASE) methodology and metadynamics simulation, as well as machine learning, to predict the biological function of newly identified opioids and binding kinetics of opioids and opioid-reversal agents. Results from these experiments aid in evaluation of existing opioid and newly emerging synthetic opioids and inform overdose prevention strategies. OCP investigators design clinical studies to examine the effects of opioids on respiratory function, giving insight on managing the respiratory depression that may occur when opioids are co-administered with other commonly prescribed medications. Through a collaborative project with Yale-Mayo CERSI, OCP investigators will use real-world data to assess variation in opioid prescribing and use for acute pain in diverse populations. Ultimately, OCP regulatory research in this space aims to mitigate adverse consequences of opioid use and protect the public from opioid-related harm.



INFORMING POLICY AND STREAMLINING DEVELOPMENT OF PEPTIDES AND PROTEINS

Current cardiac safety testing focuses on detecting drug-induced QTc prolongation as a surrogate for risk of Torsade de Pointes. The nonclinical strategy, described in ICH S7B, includes in vitro assessment of hERG block or ventricular repolarization delay and in vivo QT prolongation. Several studies have reported predictive values of ICH S7B results for clinical QTc outcomes for small molecules; none has examined peptides and proteins other than monoclonal antibodies. OCP addressed this knowledge gap by collecting information for peptides and proteins submitted to the FDA to understand mechanisms of QTc prolongation and whether the current nonclinical testing strategies under ICH S7B are adequate for these molecules. Results of hERG assays, ventricular repolarization assays, and in vivo QT assessment were compared with clinical QTc study outcomes. The results demonstrated that ICH S7B results do not predict QTc prolongation potential of these products. Lack of alignment between hERG and ventricular repolarization assay results and clinical QTc outcomes suggested that the mechanisms of QTc prolongation by some peptides and proteins are unrelated to direct cardiac ion channel block. These findings supported FDA not recommending thorough QT studies for peptides and proteins comprised of naturally occurring amino acids.

ENSURING SAFETY OF COMMONLY USED APPROVED MEDICATIONS

Nitrosamines are highly potent mutagenic carcinogens that require strict controls to limit their amounts in pharmaceuticals. However, not all nitrosamines are equally potent, and setting a single limit for all nitrosamine impurities is not justified nor practical from a manufacturing standpoint. Current practice for setting nitrosamine impurity acceptable intake limits involves identification of a single, structurally similar analog, or surrogate, that can be used to “read-across” to the untested nitrosamine impurity. However, this approach is time-consuming and hindered by the limited availability of robust surrogates. The Nitrosamines International Technical Working Group (NITWG) was initiated in 2022 with the goal of developing a more streamlined, scientifically comprehensive, chemical structure-based approach for categorical prediction of carcinogenic potency for setting nitrosamine impurity acceptable intake limits. As a part of the working group, OCP scientists led the development of a chemical structure-based predictive approach for setting nitrosamine limits based on consideration of activating and deactivating features in the nitrosamine chemical environment. This transparent, science-based approach can be rapidly deployed to assign an impurity to one of five predicted carcinogenic potency categories, where each has a corresponding acceptable intake limit. OCP was responsible for overseeing the refinement of the predictive approach in collaboration with regulators from European Medicines Agency (EMA), Health Canada, and Swissmedic and led the development of a standalone regulatory document describing the model and its implementation for direct incorporation into the guidance documents of each international regulatory authority. This predictive approach was published by EMA in July 2023 followed by FDA in August 2023. By working to achieve international regulatory adoption of a single predictive approach for setting acceptable intake limits for this carcinogenic impurity, OCP ensured safety of prescription and over-the-counter drug products.

Communication, Outreach, and Engagement

Our outreach and engagement efforts are designed to advance the science of clinical pharmacology, foster informed decision-making, and ensure optimal drug therapy. We value opportunities to share accurate, timely information to guide effective and efficient drug development, patient care, and scientific research, as well as global harmonization of regulatory policy.

OCP shares contemporary regulatory perspectives, information on approved drug therapies, and innovative scientific achievements through a variety of in-person, virtual, and direct communication channels. OCP staff communicated regulatory perspectives and state-of-the-art science through presentations at national and international forums, as well as through webinars and collaborative workshops (See Figures 7 and 8). We engaged in discussions on challenges and opportunities in dose optimization, quantitative methodologies, rare diseases, risk mitigation, population diversity, and women's health. OCP conveyed information on NDA/BLA approvals, policy updates, events, and notable scientific topics to over 95,000 subscribers of OCP's Clinical Pharmacology Corner newsletter (a free subscription service). We are committed to leveraging these communication mechanisms to connect with our stakeholders, so that our science and policies are informed by the people we serve.

OCP Communication Activities At-a-Glance

Clinical Pharmacology Corner Subscribers

Over 95,000

Presentations

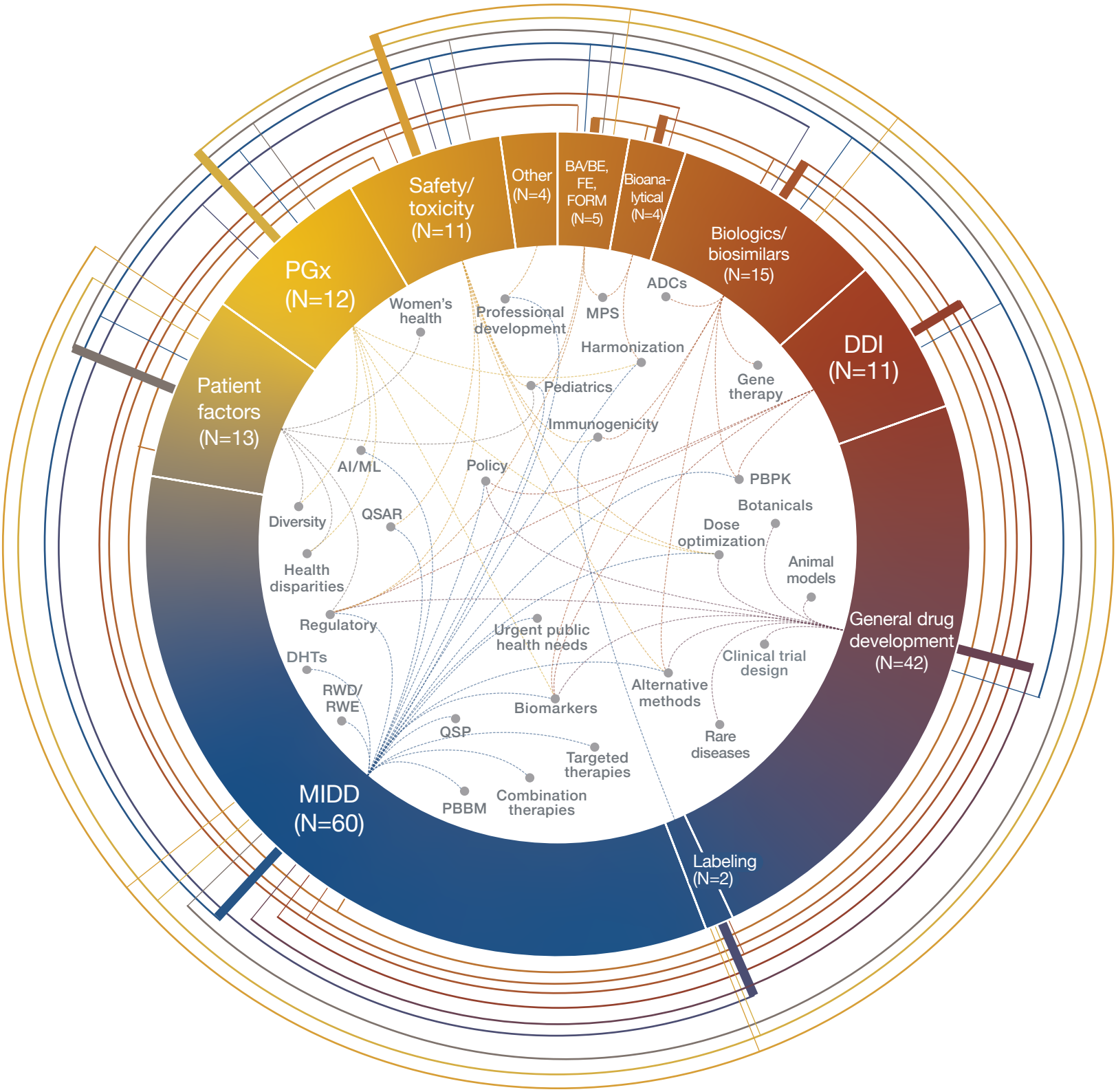
156

Workshops and Webinars

14

Figure 7.

OCP Presentation Focus Areas in 2023



Numbers represent total counts by focus area. A presentation may cover multiple focus areas; these relationships are represented by bold color lines. Dotted lines represent the various sub-topics in those areas. ADCs: antibody-drug conjugates; AI/ML: artificial intelligence/ machine learning; BA/BE: bioavailability/bioequivalence; DDI: drug-drug interaction; DHTs: digital health technologies; FE: food effects; FORM: formulation; MIDD: model-informed drug development; MPS: microphysiological systems; PBBM: physiologically based biopharmaceutics modeling; PBPK: physiologically based pharmacokinetics; PGx: pharmacogenomics; QSP: quantitative systems pharmacology; QSAR: quantitative structure-activity relationship; RWD/RWE: real-world data/real-world evidence.

ENGAGEMENT THROUGH WORKSHOPS AND WEBINARS

Public workshops and webinars provide opportunities for direct information exchange and sharing of perspectives with stakeholders. OCP led or was a significant contributor to 14 collaborative events in 2023 that brought together fellow regulators and experts from academia and drug development to deliberate on timely topics in translational science (See Figure 8).

Figure 8.

OCP Workshops and Webinars in 2023

- Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development
- Advancing the Development of Pediatric Therapeutics (ADEPT 8) on Drug Dosing in Pediatric Patients with Renal Impairment
- Application of Artificial Intelligence and Machine Learning for Precision Medicine
- Creating a Roadmap to Quantitative Systems Pharmacology-Informed Rare Disease Drug Development
- Defining 'Candy-Like' Nonprescription Drug Products
- Increasing the Efficiency of Biosimilar Development Programs--Reevaluating the Need for Comparative Clinical Efficacy Studies
- Menopause: Potential Impact on Clinical Pharmacology and Opportunities for Future Research
- Navigating Complex Waters: A Deep Dive into FDA Drug Interactions Guidances and Resources
- Overview: Clinical Pharmacology Considerations for Food Effect Studies
- Overview: Clinical Pharmacology Considerations for Neonatal Studies
- Physiologically Based Biopharmaceutics Modeling, PBBM Best Scientific Practices to Drive Drug Product Quality: Latest Regulatory and Industry Perspectives
- Rare Disease Endpoint Advancement Pilot Program Workshop: Novel Endpoints for Rare Disease Drug Development
- Using Modeling and Simulation to Evaluate the Effects of Intrinsic and Extrinsic Factors
- Using Modeling and Simulation to Select Dosages for Combination Therapies and New Indications

OCP Outreach and Engagement in 2023

PEDIATRIC-CENTRIC ENGAGEMENT

Developing drugs for pediatric patients poses unique clinical pharmacology challenges, primarily dose selection in children spanning a wide age and development range from neonates to adolescents. OCP believes that direct engagement opportunities and collaborative forums are essential for knowledge sharing to advance the field of pediatric clinical pharmacology. In 2023, OCP participated in three pediatric-focused workshops: Defining 'Candy-Like' Nonprescription Drug Products, Advancing the Development of Pediatric Therapeutics (ADEPT 8) on Drug Dosing in Pediatric Patients With Renal Impairment; and Overview: Clinical Pharmacology Considerations for Neonatal Studies. In addition to these collaborative events, OCP actively participates in The Pediatric Cluster, monthly teleconferences with international regulators to harmonize approaches in pediatric drug development. These exchanges enhance the science of pediatric trials to provide a robust ethical and scientific framework for pediatric studies. We also share the OCP PEDSCLIPS Pediatric Clinical Pharmacology Weekly Newsletter with regulatory agencies across the globe, keeping them apprised of timely pediatric-related information, including notable publications in pediatric clinical pharmacology, pediatric drug development and regulatory science news, and upcoming meetings and events related to pediatrics.

THE OPIOID CRISIS

Through communication and partnership, OCP develops strategies to combat the opioid crisis. Several of OCP's outreach, engagement, and collaborative activities in 2023 focused on challenges involving opioids and opioid-like products. Our staff shared cutting-edge applied regulatory research to address the ongoing opioid crisis via the widely attended public FDA Grand Rounds webcast series. This presentation focused on computational methods that have been developed to rapidly assess if newly emerging opioids are a risk to public safety and to evaluate dosing strategies for using opioid receptor antagonists. Through FDA's ongoing partnership with the Reagan-Udall Foundation, two public meetings were held in 2023 which focused on managing risks from misuse of opioids and opioid-like products. Workshop objectives for Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose included understanding the current landscape of fatal overdoses in the US, including changes in patterns of drug use, trends in the illicit drug supply, and real-world experience of overdose; understanding the gaps and opportunities for product development, as well as optimization of treatment of opioid-involved overdose with existing opioid overdose management products; and discussing other (non-pharmacological) public health interventions/approaches to better manage overdose, especially in the pre-hospital setting or by laypersons. The Mitigating Risks from Human Xylazine Exposure event explored real-world experiences and scientific evidence on emerging data trends for human xylazine exposure and examined concrete strategies for risk management and clinical research that directly support the mitigation and reduction of risks associated with human exposure to xylazine.

PATIENT ADVOCATE PERSPECTIVES - OCP DAY 2023

Since 1999, OCP has hosted an office-wide event to hear from experts in the field of clinical pharmacology, thought leaders in drug development, and pioneers in health care (Office of Clinical Pharmacology Science Day: A Forum to Stimulate Innovation in Clinical Pharmacology). This event offers staff a forum to share ongoing regulatory research, participate in professional development activities, and foster open dialogue on regulatory challenges encountered in their day-to-day work. This year's event, OCP Day 2023, featured keynote and panel discussions from patient advocates, who shared their invaluable experiences and lessons learned from navigating the treatment landscape for their diseases. Patient advocates shared insights on inclusion of the patient perspective in drug development and dosage optimization, what patients would benefit from knowing regarding the types of data that inform dosage and how these data are interpreted, and how patients view the efficacy-tolerability balance based on their disease. OCP heard patient experiences gained from clinical trial participation and the value of patient involvement in study design and endpoint selection. Advocates also shared perspectives on toxicities, adverse event management, and what information are helpful to patients and caregivers for informed decision-making.

2024 Outlook

Advances in basic science, translational and clinical medicine, and applied clinical pharmacology have resulted in transformative therapeutic options for patients. Despite these positive impacts of scientific innovation, more work needs to be done. We remain committed to better elucidating the sources of treatment response variability and translating that knowledge into optimized pharmacotherapy. We seek to apply science- and equity-based principles to ensure adequate inclusion of under-represented patient populations in clinical trials. We are committed to evaluating and integrating both established and emerging scientific methodologies in drug development and regulatory evaluation. We hold the needs of patients and their caregivers at the center of our collective efforts.

Our goal is singular: apply the most contemporary scientific knowledge in ways that pragmatically ensure timely access to safe and effective treatments. A clear, robust strategy is critical to achieving this objective: advance the science of clinical pharmacology, consider patient perspectives in all we do, and elevate our staff to accomplish their goals. To that end, we will continue to enhance our core interdisciplinary review processes and decision-making paradigms to bring new drugs to patients using cutting edge translational and quantitative tools. We will create opportunities to engage with patients, caregivers, and HCPs to better understand their pharmacotherapeutic needs and perspectives. For 2024, OCP has planned public workshops on topics such as development of therapeutic biologics, therapeutic drug monitoring, quantitative medicine, and dose optimization, among others. We will explore new ways to reach an even broader group of stakeholders for mutual learning and collaboration. Our Clinical Pharmacology Corner subscription service reaching over 95,000 stakeholders will deploy enhanced formats for disseminating information on notable updates and new drug approvals, and new free subscription services dedicated to quantitative and translational sciences are in the works.

Our staff members are critical to achieving these goals. We are excited about supporting their continued professional and personal development with new training and resource platforms and recognition mechanisms as they demonstrate their unparalleled commitment to public service. In addition, we envision new ways of intersecting with our colleagues throughout multiple functional areas and scientific disciplines across the U.S. FDA. These enhanced collaborations are based on guiding principles of patient-centricity, shared accountability, and scientific and regulatory synergy. Partnership is the foundation of our strategy, and we could not be more excited to carry on the work of advancing public health for the benefit of patients and communities.

Examples presented in this Annual Report are illustrative and are not a comprehensive representation of our 2023 activities and accomplishments. For comments or questions, please contact ocp@fda.hhs.gov.

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Publication Title	Citation
2022 white paper on recent issues in bioanalysis: enzyme assay validation, BAV for primary end points, vaccine functional assays, cytometry in tissue, LBA in rare matrices, complex NAb assays, spectral cytometry, endogenous analytes, extracellular vesicles part 2--recommendations on biomarkers/CDx, flow cytometry, ligand-binding assays development & validation; emerging technologies; critical reagents deep characterization.	Bioanalysis. 2023 Aug;15(15):861-903.
2022 white paper on recent issues in bioanalysis: FDA draft guidance on immunogenicity information in prescription drug labeling, LNP & viral vectors therapeutics/vaccines immunogenicity, prolongation effect, ADA affinity, risk-based approaches, NGS, qPCR, ddPCR assays (Part 3--recommendations on gene therapy, cell therapy, vaccines immunogenicity & technologies; immunogenicity & risk assessment of biotherapeutics and novel modalities; NAb assays integrated approach).	Bioanalysis. 2023 Jul;15(14):773-814.
2022 white paper on recent issues in bioanalysis: ICH M10 BMV guideline & global harmonization; hybrid assays; oligonucleotides & ADC; non-liquid & rare matrices; regulatory inputs (Part 1A--recommendations on mass spectrometry, chromatography and sample preparation, novel technologies, novel modalities, and novel challenges, ICH M10 BMV guideline & global harmonization; Part 1B--regulatory agencies' inputs on regulated bioanalysis/BMV, biomarkers/CDx/BAV, immunogenicity, gene & cell therapy and vaccine).	Bioanalysis. 2023 Aug;15(16):955-1016.
A bioanalytical method for quantification of N-nitrosodimethylamine (NDMA) in human plasma and urine with different meals and following administration of ranitidine.	J Pharm Sci. 2023 May;112(5):1315-23.
A comprehensive regulatory and industry review of modeling and simulation practices in oncology clinical drug development.	J Pharmacokinet Pharmacodyn. 2023 Jun;50(3):147-72.
A metagenomic analysis for combination therapy of multiple classes of antibiotics on the prevention of the spread of antibiotic-resistant genes.	Gut microbes. 2023 Dec;15(2):2271150.
A multistakeholder perspective on advancing individualized therapeutics.	Clin Pharmacol Ther. 2023 Nov;114(5):994-1001.
A Phase-I pharmacokinetic, safety and food-effect study on flubentylosin, a novel analog of Tylosin-A having potent anti-Wolbachia and antifilarial activity.	PLoS Negl Trop Dis. 2023 Jul 10;17(7):e0011392
A survey of FDA Approved Monoclonal Antibodies and Fc-fusion Proteins for Manufacturing Changes and Comparability Assessment.	Pharm Res. 2023 Nov 1. doi: 10.1007/s11095-023-03627-5. Online ahead of print.
A win ratio approach for comparing crossing survival curves in clinical trials.	J Biopharm Stat. 2023 Jul 4;33(4):488-501.
Achieving big with small: quantitative clinical pharmacology tools for drug development in pediatric rare diseases.	J Pharmacokinet Pharmacodyn. 2023 Dec;50(6):429-444.

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Publication Title	Citation
Addressing the knowledge gaps for providing optimal drug pharmacotherapy for the obese.	J Clin Pharmacol. 2023 Nov:63 Suppl 2:S6-S7.
Advancing innovations in biosimilars.	Clin Pharmacol Ther. 2023 Jan;113(1):11-5.
Adverse events in pregnant patients treated with coronavirus disease 2019 therapeutics.	J Med Toxicol. 2023 Oct;19(4):381-388.
Alternative trastuzumab dosing schedules are associated with reductions in health care greenhouse gas emissions.	JCO Oncol Pract. 2023 Sep;19(9):799-807.
Animal pharmacokinetics/pharmacodynamics (PK/PD) infection models for clinical development of antibacterial drugs: lessons from selected cases.	J Antimicrob Chemother. 2023 Jun;78(6):1337-43.
Application of quantitative systems pharmacology to pediatric drug safety assessment.	Clin Pharmacol Ther. 2023 Oct;114(4):748-750.
Artificial Intelligence: From Buzzword to Useful Tool in Clinical Pharmacology.	Clin Pharmacol Ther. 2023 Oct 26. doi: 10.1002/cpt.3083. Online ahead of print.
Assessing information gaps associated with initial pediatric study plans for new oncology drug and biological products.	Clin Pharmacol Ther. 2023 Sep;114(3):618-22.
Assessing pharmacokinetics in liver disease: challenges and future considerations for classification of hepatic dysfunction and use of in silico methods.	J Clin Pharmacol. 2023 Jul;63(7):755-8.
Availability of safe and effective therapeutic options to pregnant and lactating individuals following the US FDA Pregnancy and Lactation Labeling Rule.	J Pediatr. 2023 Aug;259:113342.
Biowaiver monograph for immediate-release dosage forms: levamisole hydrochloride.	J Pharm Sci. 2023 Mar;112(3):634-9.
Biowaiver monograph for immediate-release solid oral dosage forms: levocetirizine dihydrochloride.	J Pharm Sci. 2023 Apr;112(4):893-903.
Bridging of a liquid chromatography-tandem mass spectrometry method for oxytetracycline, chlortetracycline, and tetracycline in bovine kidney with the official microbial growth inhibition assay.	J AOAC Int. 2023 Jan-Feb;106(1):73-87.
Canine intestinal organoids as a novel in vitro model of intestinal drug permeability: a proof-of-concept study.	Cells. 2023 Apr 27;12(9):1269.
Clinical lactation studies of neuropsychiatric medications: clinical pharmacology and labeling considerations.	J Clin Pharmacol. 2023 Jun;63 Suppl 1:S159-69.
Clinical pharmacology of RNAi-based therapeutics: a summary based on FDA-approved small-interfering RNAs.	Drug Metab Dispos. 2023 Feb 1;51(2):193-8.
Combined oral contraceptives as victims of drug interactions.	Drug Metab Dispos. 2023 Jun;51(6):718-32.
Coming full circle: the potential utility of real-world evidence to discern predictions from a physiologically based pharmacokinetic model.	Biopharm Drug Dispos. 2023 Aug;44(4):344-7.

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Computational model of in vivo corneal pharmacokinetics and pharmacodynamics of topically administered ophthalmic drug products.	Pharm Res. 2023 Apr;40(4):961-75.
Considerations and challenges in the remdesivir COVID-19 pediatric development program.	J Clin Pharmacol. 2023 Feb;63(2):259-65.
Considerations for use of pharmacodynamic biomarkers to support biosimilar developmen--(I) a randomized trial with PCSK9 inhibitors.	Clin Pharmacol Ther. 2023 Jan;113(1):71-9.
Considerations for use of pharmacodynamic biomarkers to support biosimilar development--(II) a randomized trial with IL-5 antagonists.	Clin Pharmacol Ther. 2023 Jan;113(1):80-9.
Considerations for use of pharmacodynamic biomarkers to support biosimilar development--(III) a randomized trial with interferon beta-1a products.	Clin Pharmacol Ther. 2023 Feb;113(2):339-48.
Considerations from an International Regulatory and Pharmaceutical Industry (IQ MPS Affiliate) Workshop on the Standardization of Complex In Vitro Models in Drug Development.	Adv Biol (Weinh). 2023 Oct 9:e2300131. doi: 10.1002/adbi.202300131. Online ahead of print.
Correction to: Training the next generation of pharmacometric modelers: a multisector perspective.	J Pharmacokinet Pharmacodyn. 2023 Sep 5. doi: 10.1007/s10928-023-09885-5. Online ahead of print.
Creating a Roadmap to Quantitative Systems Pharmacology-Informed Rare Disease Drug Development: A Workshop Report.	Clin Pharmacol Ther. 2023 Nov 20. doi: 10.1002/cpt.3096. Online ahead of print.
Current state and challenges of physiologically based biopharmaceutics modeling (PBBM) in oral drug product development.	Pharm Res. 2023 Feb;40(2):321-36.
Current Status and Future Directions: The Application of Artificial Intelligence/Machine Learning for Precision Medicine.	Clin Pharmacol Ther. 2023 Dec 16. doi: 10.1002/cpt.3152. Online ahead of print.
Deep learning-enabled natural language processing to identify directional pharmacokinetic drug-drug interactions.	BMC bioinformatics. 2023 11 01;24(1):413.
Designing dose-optimization studies in cancer drug development: discussions with regulators.	Stat Biopharm Res. 2023; 15(3): 697-703.
Developing a mechanistic understanding of the nonlinear pharmacokinetics of letermovir and prospective drug interaction with everolimus using physiological-based pharmacokinetic modeling.	Clin Transl Sci. 2023 Jun;16(6):1039-48.
Developing Therapy for Every Kid With Cancer - Summary of a Scientific Session at the 2023 ASCPT Meeting.	Clin Pharmacol Ther. 2023 Nov 24. doi: 10.1002/cpt.3101. Online ahead of print.
Development of a Generic Fetal Physiologically Based Pharmacokinetic Model and Prediction of Human Maternal and Fetal Organ Concentrations of Cefuroxime.	Clin Pharmacokinet. 2023 Nov 14. doi: 10.1007/s40262-023-01323-6. Online ahead of print.
Development of mouse models with restricted HLA-B*57:01 presentation for the study of flucloxacillin-driven T-cell activation and tolerance in liver injury.	J Allergy Clin Immunol. 2023 Aug;152(2):486-99.e7.

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Publication Title	Citation
Development of polarization-sensitive optical coherence tomography imaging platform and metrics to quantify electrostimulation-induced peripheral nerve injury in vivo in a small animal model.	Neurophotonics. 2023 Apr;10(2):025004.
Diagnostic performance of circulating biomarkers for non-alcoholic steatohepatitis.	Nat Med. 2023 Sep 7;29:2656–2664. Epub ahead of print.
Digital technologies: innovations that transform the face of drug development.	Clin Transl Sci. 2023 Aug;16(8):1323-30.
Dissolution-hollow fiber membrane (D-HFM) system to anticipate biopharmaceutics risk of tablets and capsules.	J Pharm Sci. 2023 Mar;112(3):751-9.
Diversity in clinical pharmacology: a call to action.	Clin Pharmacol Ther. 2023 Mar;113(3):483-5.
Dose selection for biological enzyme replacement therapy indicated for inborn errors of metabolism.	Clin Transl Sci. 2023 Dec;16(12):2438-2457.
Drug permeability--best practices for biopharmaceutics classification system (BCS)-based biowaivers: a workshop summary report.	J Pharm Sci. 2023 Jul;112(7):1749-62.
Effect of Obesity on the Pharmacokinetics and Pharmacodynamics of Anticancer Agents.	J Clin Pharmacol. 2023 11;63 Suppl 2:S85-S102.
Effect of omeprazole administration on the pharmacokinetics of oral extended-release nifedipine in healthy subjects.	Clin Pharmacol Ther. 2023 Nov;114(5):1134-1141.
Establishing the suitability of model-integrated evidence to demonstrate bioequivalence for long-acting injectable and implantable drug products: summary of workshop.	CPT Pharmacometrics Syst Pharmacol. 2023 May;12(5):624-30.
Evaluating pneumonitis incidence in patients with non-small cell lung cancer treated with immunotherapy and/or chemotherapy using real-world and clinical trial data.	Cancer Res Commun. 2023 Feb 1;3(2):258-66.
Evaluating the utility of proteomics for the identification of circulating pharmacodynamic biomarkers of IFNbeta-1a biologics.	Clin Pharmacol Ther. 2023 Jan;113(1):98-107.
Evaluation of truncated AUC as an alternative measure to assess pharmacokinetic comparability in bridging biologic-device using prefilled syringes and autoinjectors.	J Clin Pharmacol. 2023 Dec;63(12):1417-1429.
Exploring the knowledge gaps in infant drug exposure from human milk: a clinical pharmacology perspective.	J Clin Pharmacol. 2023 Mar;63(3):273-6.
External control arms: we're not on cruise control yet.	Clin Pharmacol Ther. 2023 Aug;114(2):249-51.
Extrapolation of adult efficacy data to pediatric systemic lupus erythematosus.	J Clin Pharmacol. 2023 Jan;63(1):105-18.
FDA approval summary for lonafarnib (Zokinvy) for the treatment of Hutchinson-Gilford progeria syndrome and processing-deficient progeroid laminopathies.	Genet Med. 2023 Feb;25(2):100335.

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Publication Title	Citation
FDA approval summary: alpelisib for PIK3CA-related overgrowth spectrum (PROS).	Clin Cancer Res. 2023 Aug 25. Epub ahead of print.
FDA approval summary: amivantamab for the treatment of patients with non-small cell lung cancer with EGFR exon 20 insertion mutations.	Clin Cancer Res. 2023 Sep 1;29(17):3262-6.
FDA approval summary: dabrafenib in combination with trametinib for BRAF V600E mutation-positive low-grade glioma.	Clin Cancer Res. 2023 Aug 23:CCR-23-1503.
FDA approval summary: futibatinib for unresectable advanced or metastatic, chemotherapy refractory intrahepatic cholangiocarcinoma with FGFR2 fusions or other rearrangements.	Clin Cancer Res. 2023 Oct 13;29(20):4027-4031.
FDA Approval Summary: Ivosidenib in Combination with Azacitidine for Treatment of Patients with Newly Diagnosed Acute Myeloid Leukemia with an IDH1 Mutation.	Clin Cancer Res. 2023 Nov 27. doi: 10.1158/1078-0432.CCR-23-2234. Online ahead of print.
FDA approval summary: lutetium Lu 177 vipivotide tetraxetan for patients with metastatic castration-resistant prostate cancer.	Clin Cancer Res. 2023 May 1;29(9):1651-7.
FDA Approval Summary: Mirvetuximab Soravtansine-Gynx for FR -Positive, Platinum-Resistant Ovarian Cancer.	Clin Cancer Res. 2023 Oct 2;29(19):3835-3840.
FDA approval summary: mobocertinib for metastatic non-small cell lung cancer with EGFR exon 20 insertion mutations.	Clin Cancer Res. 2023 Feb 1;29(3):508-12.
FDA Approval Summary: Olaparib in Combination With Abiraterone for Treatment of Patients With BRCA-Mutated Metastatic Castration-Resistant Prostate Cancer.	J Clin Oncol. 2023 Dec 21:JCO2301868. doi: 10.1200/JCO.23.01868. Online ahead of print.
FDA approval summary: pemigatinib for previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or other rearrangement.	Clin Cancer Res. 2023 Mar 1;29(5):838-42.
FDA approval summary: ripretinib for advanced gastrointestinal stromal tumor.	Clin Cancer Res. 2023 Jun 1;29(11):2020-4.
FDA approval summary: selpercatinib for the treatment of advanced RET fusion-positive solid tumors.	Clin Cancer Res. 2023 Sep 15;29(18):3573-3578.
FDA approval summary: tremelimumab in combination with durvalumab for the treatment of patients with unresectable hepatocellular carcinoma.	Clin Cancer Res. 2023 Sep 7. doi: 10.1158/1078-0432.CCR-23-2124. Online ahead of print.
FDA approval summary: tucatinib with trastuzumab for advanced unresectable or metastatic, chemotherapy refractory, HER2 positive RAS wild type colorectal cancer.	Clin Cancer Res. 2023 Nov 1;29(21):4326-4330.
FDA Public Workshop Summary-Addressing Challenges in Inhaled Antifungal Drug Development.	Clin Infect Dis. 2023 10 06:ciad607. doi:10.1093/cid/ciad607. PMID: 37802928.
Fine-tuning BERT for automatic ADME semantic labeling in FDA drug labeling to enhance product-specific guidance assessment.	J Biomed Inform. 2023 Feb;138:104285.

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Publication Title	Citation
Fine-tuning the relevance of molecular targets to pediatric cancer: addressing additional layers of complexity.	Clin Pharmacol Ther. 2023 May;113(5):957-9.
Flucloxacillin worsens while imipenem-cilastatin protects against vancomycin induced kidney injury in a translational rat model.	Br J Pharmacol. 2023 Sep 11. doi: 10.1111/bph.16234. Online ahead of print.
Food and Drug Administration public workshop summary--development considerations of antifungal drugs to address unmet medical need.	Clin Infect Dis. 2023 Aug 1;77(3):380-7.
Future opportunities in drug development: American Society for Clinical Pharmacology and Therapeutics pharmacometrics and pharmacokinetics community vision.	Clin Pharmacol Ther. 2023 Sep;114(3):507-10.
Generic lamotrigine extended-release tablets are bioequivalent to innovator drug in fully replicated crossover bioequivalence study.	Epilepsia. 2023 Jan;64(1):152-61.
Genetic and non-genetic factors influencing efavirenz population pharmacokinetics among human immunodeficiency virus-1-infected children in Ethiopia.	CPT Pharmacometrics Syst Pharmacol. 2023 Jun;12(6):783-94.
ICH S7B In Vitro Assays Do Not Address Mechanisms of QTc Prolongation for Peptides and Proteins - Data in Support of Not Needing Dedicated QTc Studies.	Clin Pharmacol Ther. 2023 Dec;114(6):1332-1341.
Identification of bradycardia following remdesivir administration through the US Food and Drug Administration American College of Medical Toxicology COVID-19 toxic pharmacovigilance project.	JAMA Netw Open. 2023 Feb;6(2):e2255815.
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Improved GSimp: a flexible missing value imputation method to support regulatory bioequivalence assessment.	Ann Biomed Eng. 2023 Jan;51(1):163-73.
In memoriam: Varsha Bhatt-Mehta, PharmD, MS, FCCP.	J Clin Pharmacol. 2023; 63(S2):S8-S9.
Inclusion of Subjects who are Obese in Drug Development: Current Status and Opportunities.	J Clin Pharmacol. 2023 Nov:63 Suppl 2:S10-S17.
Increasing impact of quantitative methods and modeling in establishment of bioequivalence and characterization of drug delivery.	CPT Pharmacometrics Syst Pharmacol. 2023 May;12(5):552-5.
Informing a comprehensive risk assessment of infant drug exposure from human milk: application of a physiologically based pharmacokinetic lactation model for sotalol.	J Clin Pharmacol. 2023 Jun;63 Suppl 1:S106-16.
Innovations in pediatric therapeutics development: principles for the use of bridging biomarkers in pediatric extrapolation.	Ther Innov Regul Sci. 2023 Jan;57(1):109-20.
Innovations, Opportunities, and Challenges for Predicting Alteration in Drug-Metabolizing Enzyme and Transporter Activity in Specific Populations.	Drug Metab Dispos. 2023 Dec;51(12):1547-1550.

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Integration of biorelevant pediatric dissolution methodology into PBPK modeling to predict in vivo performance and bioequivalence of generic drugs in pediatric populations: a carbamazepine case study.	AAPS J. 2023 Jun 29;25(4):67.
Landscape analysis of the application of artificial intelligence and machine learning in regulatory submissions for drug development from 2016 to 2021.	Clin Pharmacol Ther. 2023 Apr;113(4):771-4.
Landscape and regulatory perspective on oncology drugs in pregnancy.	J Clin Pharmacol. 2023 Jun;63 Suppl 1:S170-5.
Lessons learned from regulatory submissions involving endogenous therapeutic analyte bioanalysis.	Bioanalysis. 2023 Dec 13. doi: 10.4155/bio-2023-0209. Online ahead of print.
Leveraging clinical pharmacology data to assess biosimilarity and interchangeability of insulin products.	Clin Pharmacol Ther. 2023 Apr;113(4):794-802.
Making the case for precision dosing: visualizing the variability of cefepime exposures in critically ill adults.	J Antimicrob Chemother. 2023 Sep;78(9):2170-4.
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OCP Publications for 2023

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Publication Title	Citation
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