U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research | Office of Translational Sciences

Office of Clinical Pharmacology

2022 Annual Report

Achieving Therapeutic Individualization THROUGH INNOVATION

January 2023

www.fda.gov

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Director's Message

The word ***innovate*** comes from the Latin ***innovare*** and has, at its root, not just the suggestion of newness, but also of renewal and restoration. While "innovation" conjures images of scientific and technological advances, it is the continually renewed commitment to translating those advances into improved human health and well-being that is at the heart of our interests at the U.S. Food and Drug Administration (FDA) Office of Clinical Pharmacology (OCP). We strive to be at the forefront of innovation, working collaboratively to combine state-of-the-art translational science with rigorous regulatory assessment. Patient centricity is at the very core of this enterprise. In these pages, you will learn more about how OCP staff have embedded principles of innovation into every aspect of our work.

One of OCP's many accomplishments in 2022 was the completion of our strategic plan, OCP's Roadmap to 2025, which will act as a guide in making values-focused decisions that ultimately accelerate the science of clinical pharmacology and translational medicine and advance public health. The development of this plan was community- and data-driven, ensuring that our strategic plan is timely and relevant. You will find critical elements for innovation in our strategic plan, including collaboration, scientific excellence, staff development, communication, and engagement with patients and healthcare providers.

OCP's innovative work also led to the codification of several scientific and regulatory programs in the Prescription Drug User Fee Act VII (PDUFA VII), including one of our flagship programs, the Model-Informed Drug Development (MIDD) Paired Meeting Program. During the pilot of this program, OCP accelerated the development of drug products through use of quantitative models that leveraged physiological, disease process, and pharmacology data to help select or refine dosing regimens, plan or simulate clinical trials, and predict safety outcomes. Through their focused dedication throughout the pilot, OCP staff ensured these innovative approaches to answering critical drug development questions will continue to be available and speed the availability of drug products to patients. OCP also ensured readiness for heavy involvement in other new PDUFA programs involving innovative technologies and programs such as real-world evidence, accelerated regulatory review for certain efficacy supplements, and treatments for rare diseases.

The pages that follow are but a sample of the incredible work of a staff whose passionate commitment to excellence cannot be understated. I am optimistic and excited for the future of innovation in clinical pharmacology and translational medicine. I also continue to be in awe of this exceptional staff with its steadfast focus on therapeutic advancement for the benefit of patients.

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

Organization

OCP is a dynamic, purpose-driven organization dedicated to promoting and protecting global public health through the application of clinical pharmacology and translational medicine principles. 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, chemists, physicians, nurses, project and program managers, and administrative professionals. This diversity in expertise is our strength, guiding our work to reflect the contributions of our multidisciplinary organization and enabling us to achieve our mission and vision (See Figure 1).

Our Mission

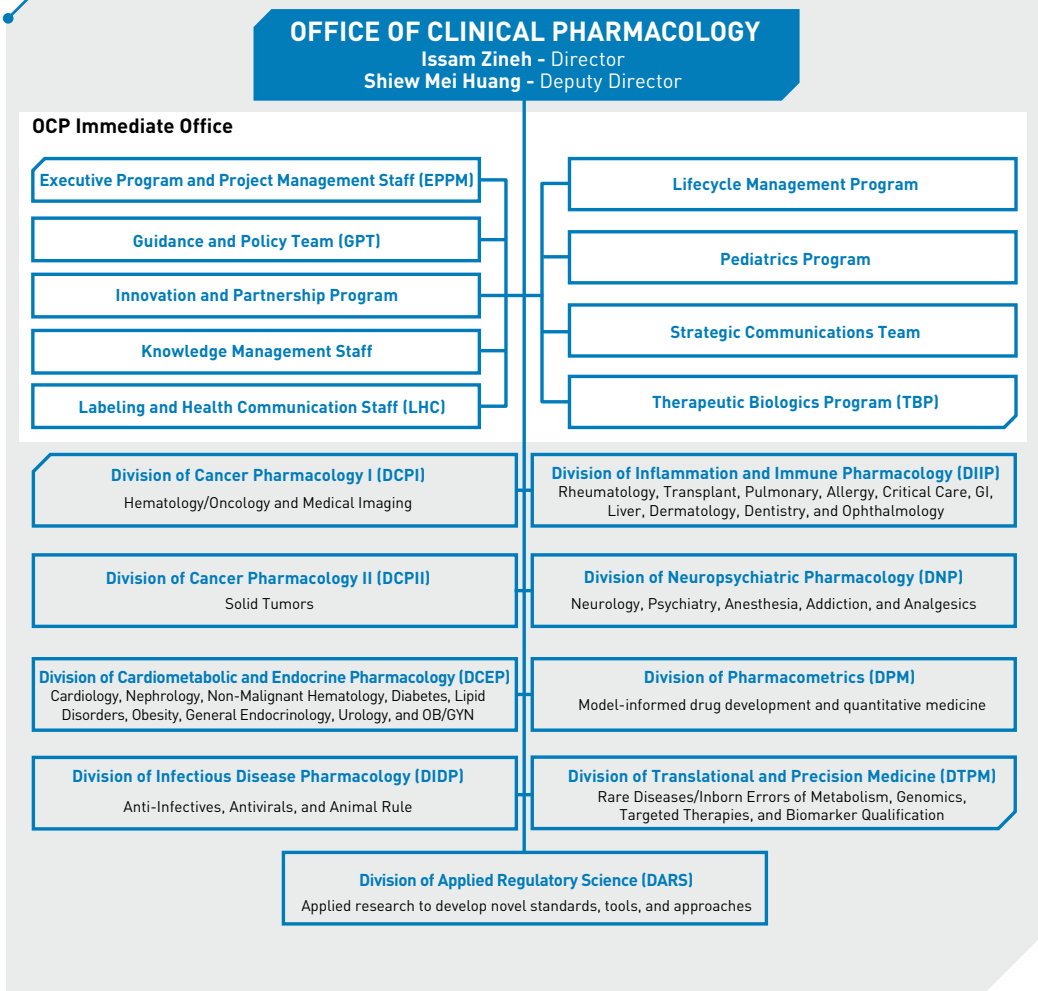
Advance the development of innovative new medicines by applying state-of-the-art scientific principles

Promote therapeutic optimization and individualization through best practices in research, policy development, and drug evaluation throughout the product lifecycle

Our Vision

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

Figure 1. **OCP Organizational Structure**



OCP fulfills its mission through its core functions of regulatory drug evaluation, policy development and implementation, and research. Outcomes in these functional areas are enhanced by our expansive communication, stakeholder engagement, and outreach on national and international levels.

We embrace our core values - stewardship, leadership, excellence, connectedness, diversity and respect - which foster a culture that empowers our staff members to translate knowledge for the benefit of patients. These core values continued to drive our strategic priorities for 2023 and beyond (See Figure 2).

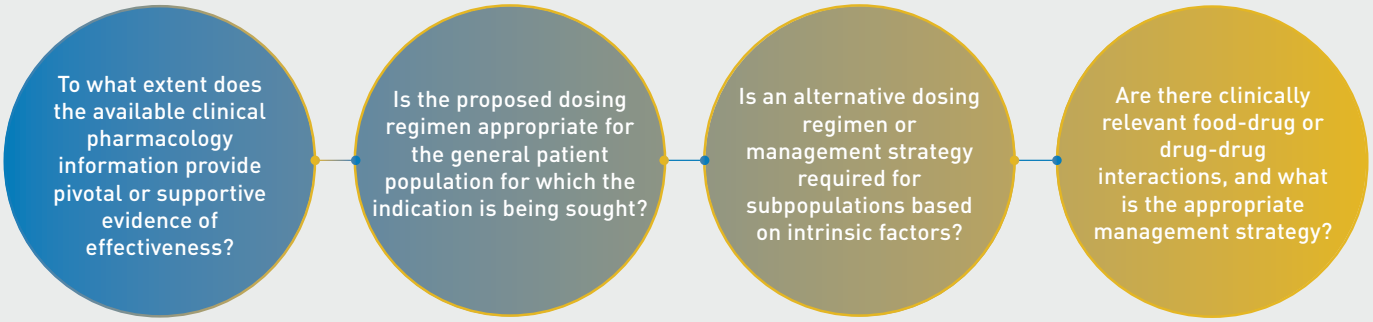
Figure 2. **OCP Roadmap to 2025** - A Values-Driven Plan

Regulatory Drug Evaluation

The mission of FDA's CDER is to ensure safe and effective drugs are available to the American people. This mission necessitates a rigorous evaluation process, bringing diverse disciplines and their expertise together to weigh the benefits and potential risks of an investigational drug product. OCP's regulatory evaluation process aligns with this goal, ensuring that approved drugs and biologics are administered at the right doses to the right patients at the right time in their disease process.

Clinical pharmacology is a multidisciplinary science, and our reviews synthesize information from all relevant clinical pharmacology knowledge areas, including drug disposition, pharmacology and biomarkers, quantitative methods, drug safety, pharmacotherapy, and clinical trial methods. We use this evidence to inform our regulatory decisions (e.g., approvability, labeling, post-approval requirements, and product lifecycle management). OCP employs an efficient, multi-disciplinary, issue-based assessment strategy to guide drug evaluation (See Figure 3). Our staff assess clinical pharmacology information in applicant submissions, integrating these data with 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 innovative scientific approaches that can practically address these knowledge gaps. Additionally, OCP explores novel ways to increase the efficiency of drug evaluation through automation and analytics, as well as provide staff with enhanced experiences across therapeutic areas. The therapeutic challenges of 2022 required inspired thinking to inform our review activities, leading to greater understanding of disease processes and meaningful outcomes to further elucidate drug effect.

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



From the preclinical phase to the post-approval phase, OCP strives to advance development of new and innovative drug therapies and promote optimization of use of these therapies. In 2022, we conducted over 5500 reviews of investigational new drug (IND) submissions to facilitate drug development, and 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 37 safe and effective new drugs and biological products to patients in 2022 (See Table 1 and Figure 4).

Table 1.

OCP Contributions to Novel Drug and Biologic Approvals

THERAPEUTIC AREA	DRUG NAME	PRIMARY REVIEW CONTRIBUTION				
		Optimized dosing regimen	Mitigated risk	Assessed genetic factors	Evaluated/proposed bridging or extrapolation strategies	Influenced development plan or trial design
Cardiology/ Hematology/ Nephrology	Camzyos	●	●	●		
	Enjaymo	●	●			
	Pyrukynd	●	●			
	Rolvedon	●	●			
	Terlivaz	●	●			
	Vonjo	●	●			
Infectious Disease	Sunlenca	●	●		●	
	Vivjoa	●	●			
	Voquezna	●		●		
Inflammation/ Immunology/ Dermatology	Cibinqo	●	●	●		
	NexoBrid		●			
	Sotyktu	●	●			
	Spevigo	●	●	●		
	Vtama	●	●			
Medical Imaging	Elucirem	●	●			
Metabolic/ Endocrine	Mounjaro	●	●			
	Tzield	●			●	
	Xenpozyme	●	●	●	●	●
Neurology/ Psychiatry	Amvuttra	●	●	●		
	Briumvi	●	●			
	Quviviq	●	●			
	Relyvrio	●	●			
	Ztalmy	●	●			
Oncology	Elahere	●	●			●
	Imjudo	●	●			
	Kimmtrak	●	●			
	Krazati	●	●			●
	Lunsumio	●	●			
	Lytgobi	●	●	●		
	Opdualag	●				
	Pluvicto	●	●			
	Rezlidhia	●	●			
	Tecvayli	●	●			
Opthalmology	Omlonti	●	●			
	Vabysmo	●	●			

Products with minimal to no systemic availability are not listed (Daxxify and Xenoview).

Figure 4.

Clinical Pharmacology Review - Innovation at Work

OPTIMIZING DOSING FOR PATIENTS

In 2022, OCP staff ensured that approved dosing regimens were safe and effective not just for the general population, but also for specific, often more vulnerable populations, including pediatric patients and those with renal or hepatic impairment. Quantitative analytical methods including **population pharmacokinetic analyses, exposure-response analyses, and modeling and simulations (M&S)** helped identify populations in need of dosage adjustments. These methods informed alternate dosing schedules, body weight-based dosing strategies, or dosing based on genetic alterations to optimize the benefit/risk profile of the drug. When appropriate, postmarketing requirements (PMRs) or postmarketing commitments (PMCs) were issued to collect additional data to support the most appropriate dosing regimen for a specific population.

MITIGATING RISK TO PATIENTS

Dosing adjustments can often mitigate or prevent undue safety risks to patients, thereby expanding the utility of the drug to patients who otherwise might not tolerate certain adverse events and improving the patient treatment experience and outcomes. With the help of approaches such as **exposure-response modeling** and **physiologically based pharmacokinetic (PBPK) analyses**, OCP staff identified potential safety issues, provided recommendations to mitigate or avoid safety events, and ensured the appropriate labeling language was articulated for healthcare providers. In 2022, OCP staff evaluated and addressed numerous potential safety events, including drug-drug and food-drug interactions, QTc interval prolongation, and immunogenicity, recommending PMRs or PMCs where appropriate.

EXPANDING TREATMENT ACCESS FOR CHILDREN AND ADOLESCENTS

Information to support drug efficacy and safety in pediatric patients is often lacking at the time of submission of a drug application, leading to deficient labeling information for children. Innovative methods to extrapolate dosing from one patient population to another is a critical component of the OCP review. OCP staff assess similarities in disease pathophysiology between adults and children, disease manifestations, drug mechanism of action, pharmacokinetics, pharmacokinetic/pharmacodynamic relationships, and safety by using methodologies such as **quantitative systems pharmacology** that combine biological, drug, and clinical trial information. OCP staff successfully applied these methodologies to ensure the earlier availability of medically necessary drugs for children.

INFLUENCING DRUG DEVELOPMENT AND TRIAL DESIGN

Sometimes, clinical outcome data are challenging to obtain (e.g., in diseases with variable natural histories or in ultra-rare genetic diseases). In such cases, biomarkers have the potential to provide valuable information that may reduce uncertainty in regulatory decisions during drug development. OCP staff play a critical role in assessing the suitability of a biomarker in the totality of evidence regarding a drug's activity, safety, and efficacy. This year, OCP staff assessed **pharmacokinetic/pharmacodynamic data** to better understand the relationship between drug exposures, biomarkers, and drug safety and efficacy.

ASSESSING GENETIC FACTORS

Genetic factors can influence the safety and efficacy of drugs, including the potential to respond to a certain treatment, possible elevated risks from treatment, and susceptibility to drug interactions. OCP staff used **pharmacogenomic analyses** to assess the contribution of genetic profiles to treatment outcomes and adverse event risks. In some cases, these analyses allowed us to generalize efficacy to difficult-to-enroll patient populations, bringing effective medications to patients sooner. In cases where genetic profiles were associated with increased adverse events, a drug was excluded from certain populations to ensure the safe use of the drug.

Innovative Programs to Enhance Drug Development and Regulation

Model-Informed Drug Development

On September 30, 2022, the President signed into law PDUFA VII. PDUFA VII formalized the highly impactful, OCP-led MIDD program and initiated several pilot programs to optimize key milestones during the drug development lifecycle (See Figure 5; https://www.fda.gov/drugs/development-approval-process-drugs/development-resources).

Figure 5.

PDUFA VII Programs and Pilots with OCP Leadership and Involvement

MIDD
Model-Informed Drug Development Program
Accelerates and optimizes drug development by providing an opportunity for sponsors and the FDA to discuss MIDD approaches within a specific drug development program

RWE
Advancing Real-World Evidence Pilot
Provides a mechanism for sponsors of selected proposals to obtain earlier and enhanced Agency feedback on RWE-based approaches intended to support new labeling claims or meet post-approval study requirements

RDEA
Rare Disease Endpoint Advancement Pilot
Advances rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process

STAR
Split Real-Time Application Review Pilot
Provides a mechanism for the review of qualified priority efficacy supplements to enable earlier patient access to therapies that address an unmet medical need

OCP successfully completed all commitments related to MIDD under PDUFA VI, including but not limited to, the Paired Meeting Pilot Program, MIDD workshops, publications, guidances and polices. The continuation of the MIDD Paired Meeting Program is a result of the successful application of preclinical and clinical data with innovative exposure-based, biological, and statistical models to help facilitate decision-making in drug development and regulatory evaluation (See Figure 6). A recent publication by several pharmaceutical developers who participated in the program noted positive impact in terms of benefits to patients, clinical development time savings, and cost savings [(PMID: 33991429)].

> **"This collaboration between industry and the Agency facilitates achievement of optimizing the development of new medicines for patients."**
>
> From: Industrial Perspective on the Benefits Realized from the FDA's Model-Informed Drug Development Paired Meeting Pilot Program (Clin Pharmacol Ther. 2021 Nov;110(5):1172-1175)

Figure 6.

MIDD Pilot Program in Review

		2018	2019	2020	2021	2022	Total
	Sponsor meetings	7	15	14	11	12	59
	Internal meetings	14	36	37	25	31	143
	Written Response Only	-	1	4	6	2	13
THERAPEUTIC AREAS	Oncology	●	●	●	●	●	
	Cardiology	●	●		●	●	
	Dermatology	●	●				
	Immunology/ Inflammation	●	●		●	●	
	Infectious Disease	●		●	●	●	
	Non-Malignant Hematology		●	●	●	●	
	Neurology		●	●	●		
	Pulmonary		●	●			
	Endocrinology			●	●	●	
	Gastroenterology			●			
	Nephrology			●	●	●	
	Ophthalmology			●	●		
	Psychiatry				●	●	
	Hepatology				●		

CDER Accelerating Rare Disease Cures Program

OCP plays an essential role in bringing treatments to patients with limited or no options, many of whom face the potential for debilitating or fatal outcomes. Our staff are involved in leading the innovative CDER Accelerating Rare disease Cures (ARC) Program, which aims to speed and increase the development of effective and safe treatment options for patients with rare diseases (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cders-arc-program). We see tremendous potential for clinical pharmacology and translational medicine approaches to provide pivotal evidence in support of drug approval and dose optimization in these patients with exceedingly high unmet medical needs. This program, and the collaborations it may bring, will build on the successes of our other initiatives, such as the MIDD program, and OCP will continue to drive many advances in rare disease drug development through our review, research, and policy activities.

> **"We have so many opportunities to build a solid foundation for developing drugs to fight rare diseases, and the benefit to patients is quite direct. OCP's work is critical to characterize drug mechanisms, generate biomarker data that can inform effectiveness, optimize dosages through concentration-response modeling, and more. If we put our heads together, we can find new ways to overcome common challenges."**
>
> **Michael Pacanowski, PharmD, MPH**
> Director - Division of Translational and Precision Medicine

Drug Development Tools

Drug Development Tools (DDTs) are methods, materials, or measures that can potentially facilitate drug development, and the FDA has established qualification programs to support DDT development. One such program, the FDA Fit-for-Purpose (FFP) Initiative, provides a pathway for regulatory acceptance of dynamic tools for use in drug development programs (https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative). OCP plays a critical role in the regulatory evaluation of FFP submissions, which focuses on methods and models for dose-finding and clinical trial design. In 2022, OCP co-led the review team which deemed Empirically Based Bayesian Emax Models fit-for-purpose for dose-finding under certain conditions.

Modeling and Simulation Initiatives

Computational (in silico) M&S are powerful tools that complement traditional methods for gathering evidence – including bench-top (in vitro) testing, and animal or clinical (in vivo) studies - about products regulated by the FDA. OCP staff routinely review results from M&S studies and use M&S approaches for regulatory decision-making and to address research questions of public health importance.

OCP has a well-established history of demonstrating and promoting the value of M&S in drug development and regulatory review, as well as in policy development and implementation. In addition to the MIDD program, OCP staff members serve on FDA's Modeling and Simulation Working Group (ModSimWG) to further support the implementation of M&S in the regulatory review process across the Agency and advocate for its utility for research and regulatory decision-making. To learn more about these activities, visit the Modeling & Simulation at FDA website (https://www.fda.gov/science-research/about-science-research-fda/modeling-simulation-fda).

Spotlight: Urgent Public Health Issues

OCP prioritizes being a responsive organization in the face of urgent public health issues. We adapt promptly to the regulatory strategies necessary to combat threats, such as emerging infectious diseases and the opioid crisis, and mobilize our resources to bring rigorously evaluated therapeutic solutions to patients.

> **During a public health emergency, drug development decisions must balance the urgent need for treatments with the importance of a thorough evaluation of safety and efficacy. Tools used in OCP guide an agile process as knowledge evolves.**
>
> **Kellie S. Reynolds, PharmD**
> Director - Division of Infectious Disease Pharmacology

COVID-19

Since the COVID-19 National Public Health Emergency (PHE) was declared in 2020, OCP continues to ensure the availability of treatments for patients fighting the devastating effects of SARS-CoV-2 infection. In 2022, our review contributions expanded treatment options for COVID-19 patients in the face of emerging variants through the Emergency Use Authorization (EUA) activities for products for the treatment of COVID-19 (bebtelovimab and anakinra) and pre-exposure prophylaxis (Evusheld), and approval of immune modulators (baricitinib and tocilizumab) for certain hospitalized adults with COVID-19. OCP's focus on therapeutic challenges for COVID-19, such as dosing in pediatric patients and treatment options for evolving variants, have led to expanding treatment options across the diverse patient population. Our staff engaged developers and international regulators on leveraging available clinical trial data in pediatric populations and optimizing administration conditions. Working with colleagues across CDER, OCP is evaluating alternative development pathways to address development challenges such as difficulty in trial conduct in an ever-changing SARS-CoV-2 variant landscape.

ANAKINRA – Use of Machine Learning for Patient Population Identification

Anakinra is an interleukin-1 (IL-1) receptor antagonist. IL-1 is involved in inflammatory diseases and linked to acute severe lung inflammation in COVID-19. In November 2022, FDA issued an EUA for the treatment of COVID-19 in certain hospitalized patients at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR). The EUA was supported by the totality of scientific evidence available to FDA, including data from a randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of anakinra in adult patients with COVID-19 pneumonia who were at risk of developing severe respiratory failure. Patients were required to test positive for suPAR, a biomarker of inflammation, at levels greater than or equal to 6 ng/mL. The therapeutic challenge: suPAR testing is not readily available in the U.S. OCP review staff used artificial intelligence/machine learning algorithms to develop an alternative patient identification method to select patients most likely to have suPAR greater than or equal to 6 ng/mL based on commonly measured patient characteristics.

Monkeypox

In August of 2022, the U.S. Department of Health and Human Services (HHS) declared a PHE in response to the ongoing spread of monkeypox virus in the U.S. To combat this threat, OCP staff participated in FDA activities focused on clinical trials for therapeutics intended to prevent or treat monkeypox, evaluated existing smallpox therapies as potential therapeutics, communicated with relevant developers and other agencies (e.g., Biomedical Advanced Research and Development Authority, Centers for Disease Control and Prevention, National Institutes of Health) on treatments for monkeypox, and collaborated on regulatory research activities.

Opioid Crisis

One of the FDA's highest priorities is addressing the opioid crisis. Opioids are claiming lives at a staggering rate, and overdoses from opioids are reducing life expectancy across the nation. Additionally, according to the U.S. Department of Defense, high-potency opioids could potentially be used as chemical weapons and result in mass casualty situations. Opioid overdose is characterized by life-threatening respiratory and central nervous system depression that, if not immediately treated, may lead to significant morbidity and mortality due to irreversible hypoxic injury. OCP is addressing this crisis through the application of structural, mechanistic, and computational approaches to research and regulatory review. Our staff seeks to understand the potential risk for respiratory depression in various clinical scenarios, develop mitigation strategies for opioid overdose, and establish dosing strategies for treatment and prophylactic indications.

Assessing Respiratory Effects of Opioids with Co-Administered Drugs

OCP designed clinical studies that allowed the safe and controlled assessment of the effects of psychotropic drugs on respiratory depression when administered in combination with opioids, improving our understanding of the potential risk for respiratory depression in the hopes of reducing opioid overdoses and deaths (https://jamanetwork.com/journals/jama/fullarticle/2797225).

NALOXONE HYDROCHLORIDE AUTOINJECTOR
A Model-Informed Approval

Naloxone is a nonselective opioid receptor antagonist, with the greatest affinity for the mu-opioid receptor. If immediately administered, naloxone can reverse the life-threatening effects of an opioid overdose and prevent hypoxia-associated injury and death. In February 2022, naloxone hydrochloride injection, 10 mg was approved for use by military personnel and chemical incident responders (1) for the emergency treatment of patients 12 years of age and older where the use of high-potency opioids such as fentanyl analogues as a chemical weapon is suspected and (2) for temporary prophylaxis of respiratory and/or central nervous system depression in military personnel and chemical incident responders entering an area contaminated with high-potency opioids such as fentanyl analogues. The approval was supported by M&S analyses conducted by OCP staff demonstrating the product results in higher rates of recovery from respiratory depression when administered as soon as possible after known or suspected opioid exposure.

Policy

In 2022, a total of 13 FDA guidances were published by OCP, the greatest number of guidances published in a calendar year to date (See Figures 7 and 8). These guidances communicate scientific approaches and regulatory recommendations that have the potential to accelerate drug development and speed the delivery of safe and effective drugs to patients. Guidance topics include clinical pharmacology considerations for specific populations, in particular children and neonates; novel drug products such as antibody-drug conjugates and oligonucleotides; mass balance, food-effect, and bioavailability studies; bioanalytical method validation; safety assessments; and quantitative medicine methodologies. Furthermore, three of the guidances listed in Figure 8 below were conducted under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The recommendations in ICH guidances are considered acceptable across many regulatory agencies worldwide, streamlining global drug development and regulatory evaluation.

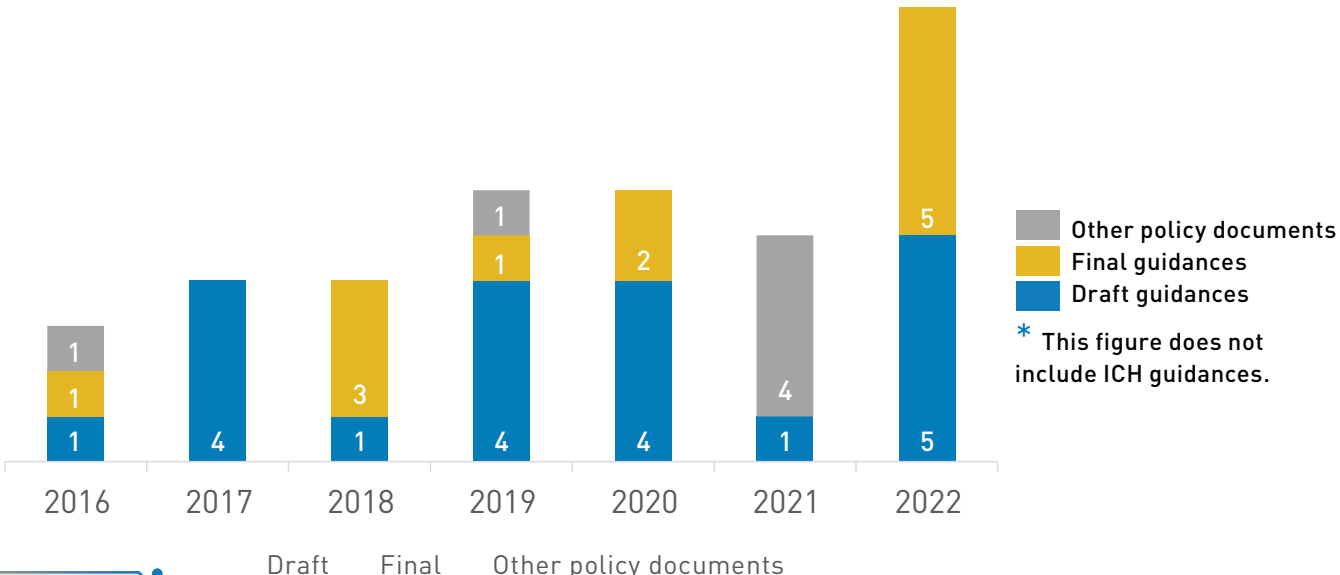
IMPACTING DRUG DEVELOPMENT FOR NEONATAL INFANTS

Given that most drugs administered in neonatal intensive care units are used off-label, it is important that drug information be obtained in neonates to address gaps in neonatal labeling. In addition, therapies should be developed for conditions unique to neonates. The FDA is the first global regulatory authority to finalize guidance on clinical pharmacology studies for neonatal infants (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-neonatal-studies-drugs-and-biological-products-guidance).

Five OCP-led guidances were finalized in 2022, bringing the total of final OCP-led guidances published since the inception of OCP's Guidance and Policy Team (GPT) in 2016 to 12. Guidance finalization is a rigorous process that includes consideration and resolution of hundreds of public comments, the addition of the most up-to-date science, and concurrence with experts across the Agency. GPT's efforts have streamlined this process resulting in reduced time to finalized guidances, bringing much needed perspectives to drug developers. Such accomplishments would not be possible without the support of our highly committed staff, who dedicated an extraordinary amount of time and effort outside of regulatory review to participate in policy-related working groups in 2022 to ensure the most recent scientific advances are integrated into FDA guidance documents.

OCP is committed to training and education of both internal and external stakeholders, ensuring that all relevant parties in drug development and approval are aware of the most up-to-date science, policies, and procedures. OCP utilized multiple education mechanisms, including a clinical pharmacology course for regulatory scientists, Lunch and Learn seminars, dedicated guidance trainings, scientific interest groups, and external webinars facilitated by the CDER's Small Business & Industry Assistance Team.

Figure 7. **OCP-Led Guidances** from 2016 to 2022*



Draft Final Other policy documents

Figure 8. **OCP Guidances Published** in 2022

SPECIFIC POPULATIONS

- General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products (Final)
- General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products (Revised draft)

NOVEL DRUG PRODUCTS

- Clinical Pharmacology Considerations for Antibody-Drug Conjugates (Draft)
- Clinical Pharmacology Considerations for the Development of Oligonucleotide Therapeutics (Draft)

PHARMACOKINETICS

- Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations (Final)
- Bioavailability Studies Submitted in NDAs or INDs – General Considerations (Final)
- Clinical Pharmacology Considerations for Human Radiolabeled Mass Balance Studies (Draft)
- M10-Bioanalytical Method Validation and Study Sample Analysis (Final)*

SAFETY

- E14/S7B IWG-Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential-Questions and Answers (Final)*
- Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling--Content and Format (Draft)
- M12-Drug Interaction Studies (Draft)*

QUANTITATIVE MEDICINE

- Pharmacokinetic-Based Criteria for Supporting Alternative Dosing Regimens of Programmed Cell Death Receptor-1 (PD-1) or Programmed Cell Death-Ligand 1 (PD-L1) Blocking Antibodies for Treatment of Patients with Cancer (Final)
- Population Pharmacokinetics (Final)

* These guidances were developed under the auspicies of ICH.

Applied Regulatory Research

Innovative research is sparked by a challenge. Whether it's an emergent public health need, a demanding regulatory question, or therapeutic problem needing a solution, OCP is on the forefront of this landscape and mobilizes our regulatory research programs to address these challenges and improve patient health. OCP's regulatory science research program is designed to advance and deploy the science of clinical pharmacology and translational medicine to ensure the quality, efficacy, and safety of drug products used by patients and consumers. Our research activities inform regulatory decision-making and contemporary policy development, and we use robust tools and approaches in new and creative ways to answer research questions. Our research enables us to better understand and assess risk, prepare for and respond to public health emergencies, and help ensure the safety of products used by patients. In 2022, 104 research projects were conducted under OCP's comprehensive research portfolio, using a variety of laboratory, computational, and translational methods, to address critical questions across a range of therapeutic needs (See Figures 9 through 11). Research outcomes and their regulatory application were conveyed to the broader scientific community through 163 publications in peer-reviewed journals in 2022 (See Figure 12 and Appendix).

Figure 9.

OCP Research At-a-Glance

109
Research fellows

$17.0M
Total research budget (approximate)

14
Average number of OCP publications per month

Figure 10.

OCP Research Highlights in 2022

URGENT PUBLIC HEALTH ISSUES

OCP responds to urgent public health needs, such as COVID-19 and the opioid crisis, by applying innovative research methodologies to advance therapeutic strategies. Our researchers use mechanistic models for viral infections to predict effective dosing regimens for combination and monotherapies to treat COVID-19. OCP utilized modeling approaches to achieve greater understanding of the potential for drug-drug interactions, liver toxicity, and the effect of patient factors for COVID-19 therapeutics and to inform safety and risk assessments for drugs repurposed for COVID-19. Additionally, OCP continues its involvement in the multidisciplinary American College of Medical Toxicology's (ACMT) Toxicology Investigators Consortium (ToxIC) pharmacovigilance and overdose surveillance and research network which tracks unlabeled adverse events in patients treated or self-medicated with approved and unapproved COVID-19 drug products. To address the opioid crisis, OCP research activities have focused on clinical trials, mechanistic pharmacodynamic modeling, and molecular simulation techniques to minimize the adverse effects of opioids on cardiac and respiratory function. OCP researchers employ the FDA Public Health Assessment via Structural Evaluation (PHASE) methodology, a computational tool that uses the molecular structure of a substance to predict its biological function in the body, to evaluate opioids and chemicals with opioid-like properties and risk these drugs may pose to public safety.

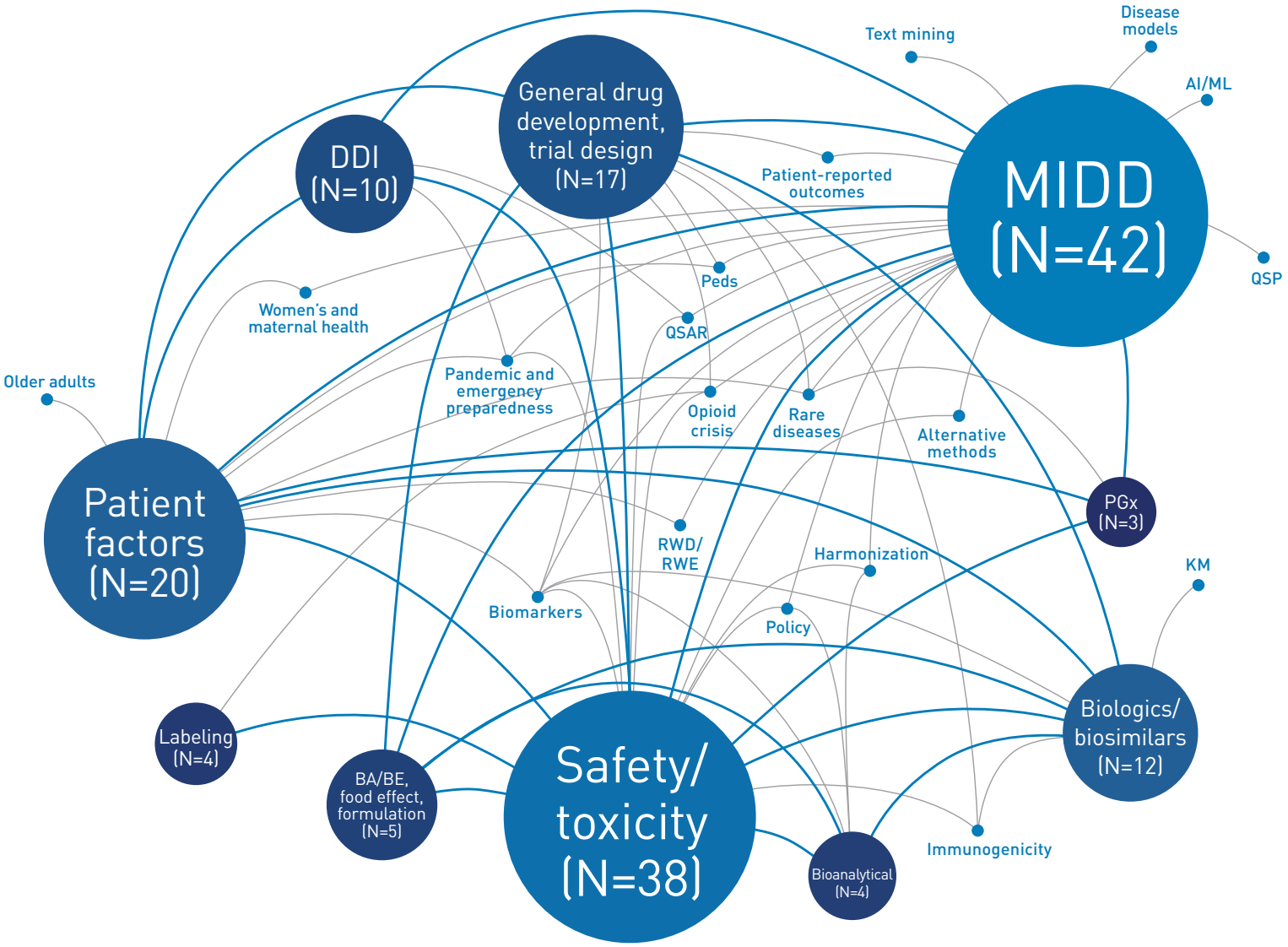
PATIENT FACTORS

Individualized therapy considers the diversity of the population and the many patient factors that can influence drug exposure and response. OCP research in this area focuses on specific populations, including pediatric populations, older adults, pregnant and lactating women, and patients with organ impairment. Researchers assimilate knowledge from clinical studies to understand differences in pharmacokinetics and pharmacodynamics across populations, identify informative endpoints, and formulate dose adjustment strategies. Model-based methods, such as quantitative systems pharmacology and PBPK, aid in assessing risk and safety profiles for pediatric patients and are being applied in research related to pregnancy PK and lactation. In addition, in vitro-in vivo extrapolation approaches have been assessed for prediction of drug transfer into human milk.

SAFETY

Managing risk for the drug products we regulate relies on a comprehensive understanding of a product's safety and toxicity profile. OCP DARS's cardiac safety evaluation program is a prime example of how OCP research informs risk management. In vitro electrophysiology studies and quantitative structure-activity relationship (QSAR) modeling are used to predict cardiac adverse effects and toxicity. OCP research partnerships are aimed at developing an in vivo/in vitro knowledge base and analysis tool to predict cardiotoxicity. Databases are being created for large molecules to determine whether studies described in ICH S7B and E14 should be applied toward these therapies. OCP also focuses on issues related to immunogenicity, including evaluating the impact of immunogenicity on interchangeability, characterizing immunogenicity of host cell proteins, and determining immunogenicity risk of biosimilar drugs in combination with other drug products. To augment laboratory and basic science research findings, OCP conducts clinical studies to fully investigate risk, such as to evaluate the potential for ranitidine to convert to N-nitrosodimethylamine (NDMA), a probable human carcinogen, in humans.

Figure 11. **OCP Research Focus Areas** in 2022



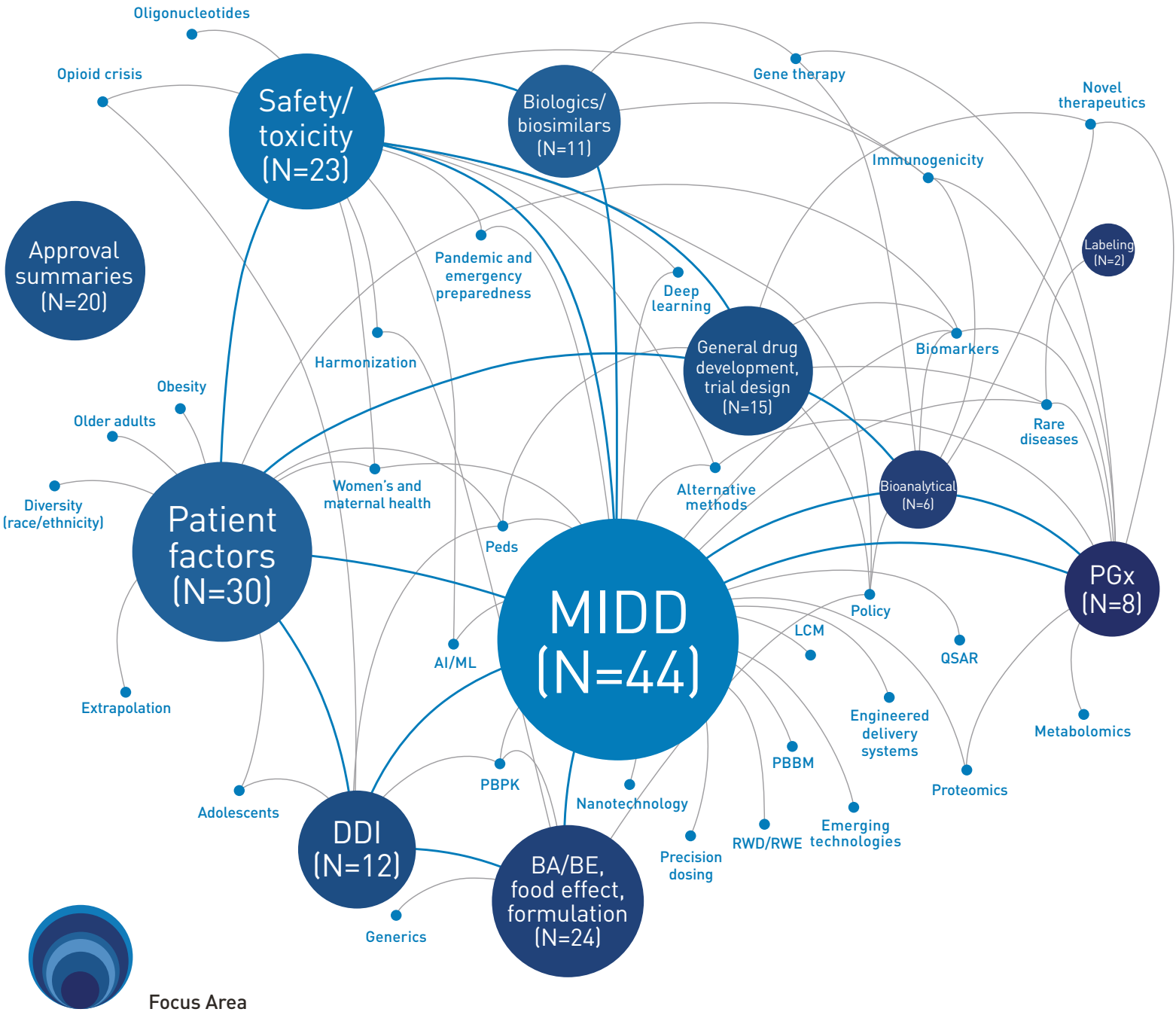
Focus Area

Subtopic

Numbers represent total counts by focus area. A research project may cover multiple focus areas; these relationships are represented by bold blue lines. Grey lines represent the various sub-topics in those areas. AI/ML: artificial intelligence/ machine learning; BA/BE: bioavailability/bioequivalence; DDI: drug-drug interaction; KM: knowledge management; LCM: lifecycle management; Peds: pediatrics; PGx: pharmacogenomics; QSP: quantitative systems pharmacology; RWD/RWE: real-world data/real-world evidence.

Figure 12.

OCP Publications Focus Areas in 2022



Numbers represent total counts by focus area. A publication may cover multiple focus areas; these relationships are represented by bold blue lines. Grey lines represent the various sub-topics in those areas. AI/ML: artificial intelligence/ machine learning; BA/BE: bioavailability/bioequivalence; DDI: drug-drug interaction; KM: knowledge management; LCM: lifecycle management; Peds: pediatrics; PGx: pharmacogenomics; QSP: quantitative systems pharmacology; RWD/RWE: real-world data/real-world evidence.

Spotlight On Innovation: Model-Based Methods

Model-based approaches use preclinical and clinical data with exposure-based, biological, and statistical models to help facilitate decision-making in the development of safe and effective drugs. These approaches leverage a range of innovative quantitative methods and have become routinely used and successfully applied to provide supportive evidence for safety and efficacy, optimize dosing, and address challenging questions during drug development. In 2022, OCP published findings in several areas where model-based methods were applied, including addressing emergent public health needs, characterizing potential biomarkers, tailoring therapies for specific populations, and understanding safety of products and combinations. Representative examples of these works appear below. See the Appendix for a complete list of OCP publications in 2022.

NOTABLE PUBLICATIONS ON MODEL-BASED METHODS

- Application of machine learning based methods in exposure-response analysis (J Pharmacokinet Pharmacodyn 2022 Aug;49(4):401-10)
- Application of population pharmacokinetic modeling, exposure-response analysis, and classification and regression tree analysis to support dosage regimen and therapeutic drug monitoring of plazomicin in complicated urinary tract infection patients with renal impairment (Antimicrob Agents Chemother 2022 Apr 19;66(4):e0207421)
- Applications, challenges, and outlook for PBPK modeling and simulation: a regulatory, industrial and academic perspective (Pharm Res 2022 Aug;39(8):1701-31)
- Concentration-response model of immediate release oxycodone drug liking by different routes of abuse (Pain Med 2022 Jul;23(7):1311-22)
- Developing an in vitro to in vivo extrapolation (IVIVE) model to predict human milk-to-plasma drug concentration ratios (Mol Pharm 2022 Jul 4;19(7):2506-17)
- Impact of switching on pharmacokinetics of therapeutic biologics and interchangeability assessment—a simulation study (J Clin Pharmacol 2022 Jan;62(1):36-45)
- Individualized patient care through model-informed precision dosing: reflections on training future practitioners (AAPS J 2022 Nov 15;24(6):117)
- Model-informed approach supporting approval of adalimumab (HUMIRA) in pediatric patients with ulcerative colitis from a regulatory perspective (AAPS J 2022 Jul 6;24(4):79)
- Model-informed drug development approaches to assist new drug development in the COVID-19 pandemic (Clin Pharmacol Ther 2022 Mar;111(3):572-8)
- Toward bridging unmet medical need in early Alzheimer's disease: an evaluation of beta-amyloid (Abeta) plaque burden as a potential drug development tool (Clin Pharmacol Ther 2022 Apr;111(4):728-31)

OCP Division of Applied Regulatory Science

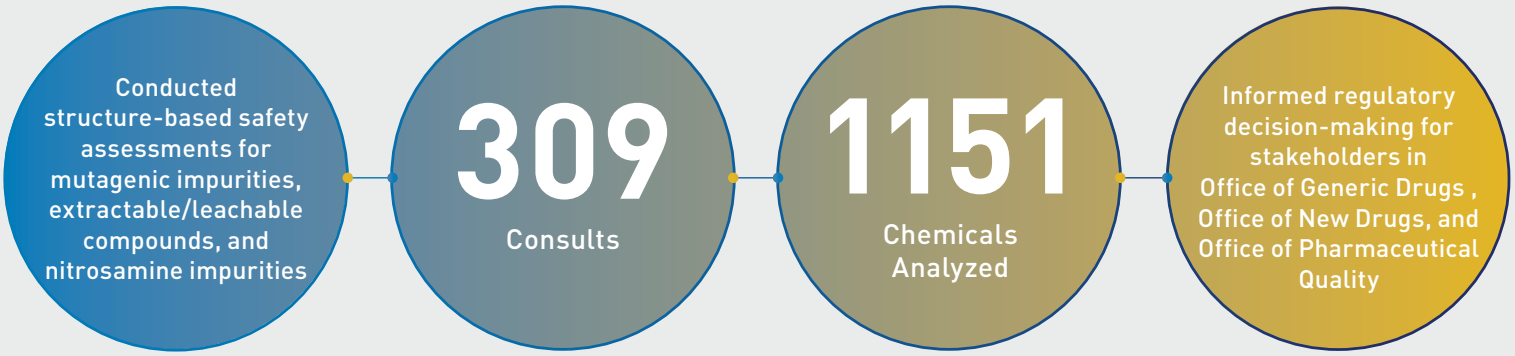
OCP's dedicated research division, DARS, specializes in the application of translational approaches such as in vitro and in vivo laboratory methods, experimental medicine, in silico computational modeling and informatics, and integrated clinical research to meet regulatory and public health challenges (See Figure 13 for an example). OCP's regulatory research activities are further enhanced by our robust research fellowship program which offered unique development opportunities to 109 new scientists in 2022.

Advances in systems biology, stem cell research, engineered tissues, and mathematical modeling are creating unique opportunities to improve the FDA's ability to predict risk and efficacy, bring FDA-regulated products to patients faster, and prevent products with increased toxicological risk from reaching patients. Also critical is the potential for these advances to replace, reduce, and/or refine animal testing. OCP staff champion the adoption of alternative methods to animal testing in the current drug development paradigm, and take an active role in targeted research and involvement in FDA's Alternative Methods Working Group (https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda). DARS staff work to develop and evaluate in vitro microphysiological systems (or organ tissue on-a-chip systems) as cell culture platforms to model human-specific physiology of tissues or organs to improve the efficiency of drug development. OCP continues to look for new areas of application of these technologies to facilitate drug development.

> **"We come up with new tools, models, and approaches that can be applied across the drug development spectrum to better predict safety and effectiveness and it's really something that others aren't doing quite like we are."**
>
> **David Strauss, MD, PhD**
> Director - Division of Applied Regulatory Science

For more details on our dedicated research division, visit the DARS website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/division-applied-regulatory-science).

Figure 13. **OCP's** Computational Toxicology Consultation Service



Communication, Outreach, and Engagement

OCP strives for accurate and timely communications with many stakeholders including drug developers, healthcare providers, patients, academia, and other government and regulatory agencies. Conveying the best, most up-to-date, reliable information, while acknowledging any uncertainties and gaps in knowledge, is imperative in building stakeholder trust.

OCP utilizes several communication channels to share current regulatory perspectives, therapeutic advances, and innovative scientific achievements across all areas of clinical pharmacology (See Figures 14 through 16). In 2022, OCP staff communicated current perspectives and innovative achievements through presentations and webinars at national and international forums. OCP's involvement in workshops was collaborative and multidimensional, as organizers, moderators, panelists, and presenters. The development topics discussed averaged over 1000 registrants per workshop. We fostered innovation and accelerated drug development through partnerships and collaborations with government and regulatory agencies, academia, drug developers, and patients on a variety of topics, including real-world data and evidence, machine learning, biological products and biosimilars, drug interactions, safety and toxicity, and more. Our direct communication mechanisms were valuable avenues for outreach. OCP's Clinical Pharmacology Corner newsletter subscription service conveys timely information on NDA/BLA approvals, policy updates, events, and notable scientific topics, reaching over 91,000 subscribers. OCP's PEDSCLIPS Pediatric Clinical Pharmacology Weekly Newsletter is disseminated to regulatory agencies across the globe. Collectively, these mechanisms were an effective communication strategy in 2022, allowing OCP to share our science informed by the voice of our stakeholders.

Figure 14.

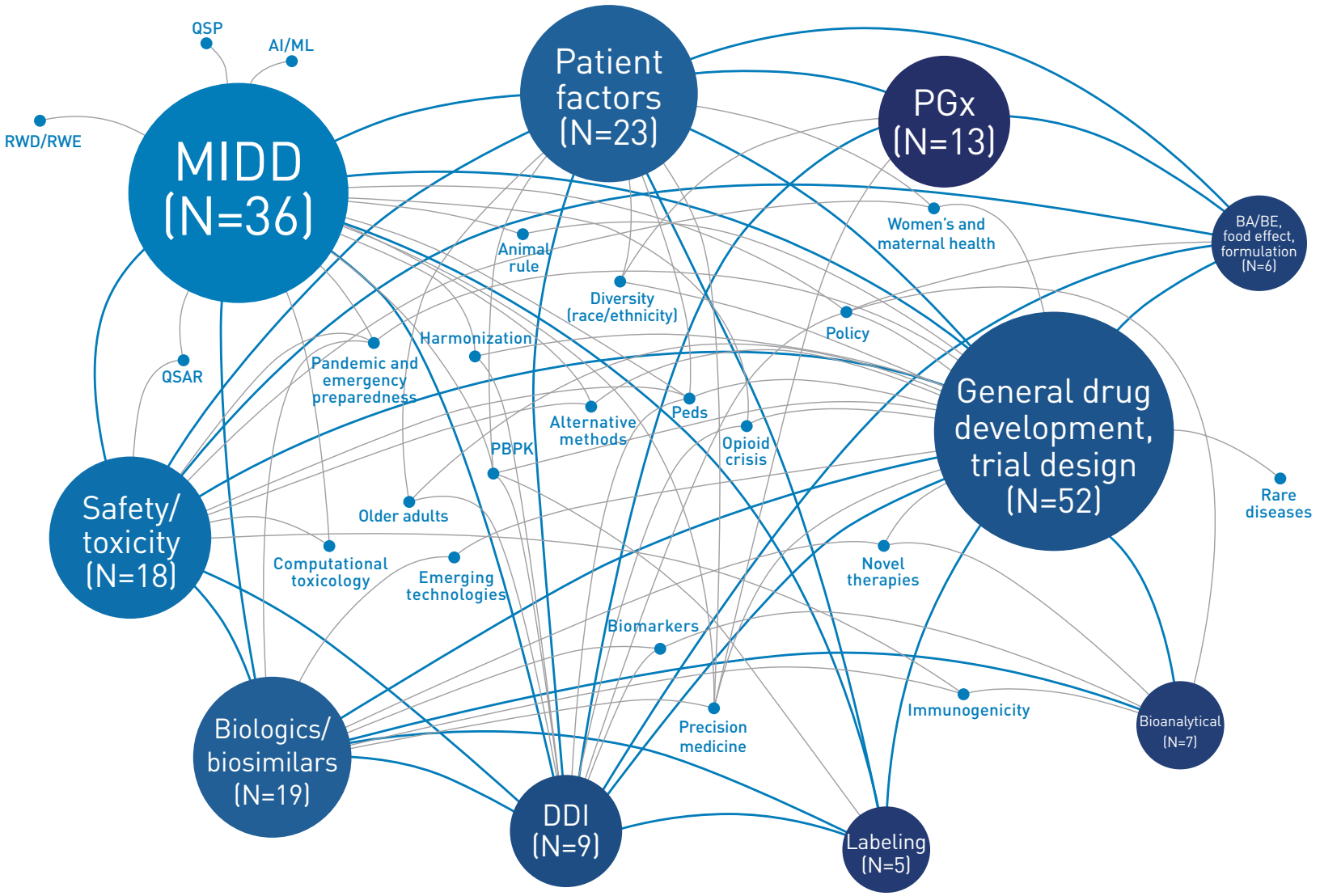
OCP Communication Activities At-a-Glance

140
Presentations

91,089
Clinical Pharmacology Corner subscribers

5
Workshops and Webinars

Figure 15. **OCP Presentation Focus Areas** in 2022



Focus Area

Subtopic

Numbers represent total counts by focus area. A presentation may cover multiple focus areas; these relationships are represented by bold blue lines. Grey lines represent the various sub-topics in those areas. AI/ML: artificial intelligence/ machine learning; BA/BE: bioavailability/bioequivalence; DDI: drug-drug interaction; KM: knowledge management; LCM: lifecycle management; Peds: pediatrics; PGx: pharmacogenomics; QSP: quantitative systems pharmacology; RWD/RWE: real-world data/real-world evidence.

Figure 16.

OCP Outreach Highlights in 2022

WORKSHOPS AND WEBINARS

OCP led five collaborative events in 2022 that brought together fellow regulators and experts from academia and industry to deliberate on timely topics in translational science:

- Pharmacokinetic Evaluation in Pregnancy
- Biosimilars: A Decade of Experience and Future Directions—Strategies for Improving Biosimilar Adoption and the Potential Role of Clinical Pharmacology
- Translational Science in Drug Development: Surrogate Endpoints, Biomarkers, and More
- Bridging Drug Efficacy and Safety to the Obese: Considerations and Scientific Approaches
- An In-Depth Look at the Final FDA Guidance: Bioavailability Studies Submitted in NDAs or INDs – General Considerations

ENGAGEMENT AND PARTNERSHIPS

Direct engagement and partnerships provide OCP an opportunity to learn the experiences, perspectives, needs, and priorities of our stakeholders, which we meaningfully incorporate into our organization's regulatory approach and strategic priorities.

- **Centers of Excellence in Regulatory Science and Innovation (CERSI) Partnerships:** OCP co-partners with several institutions under the FDA's CERSI program to foster robust and innovative approaches to advance regulatory science. Projects include studies on medication usage in older adults, assessing disparities in occurrence and outcomes of type 2 diabetes in minority populations using real-world data, identification and validation of biomarkers for breast cancer resistance; and metabolism-based drug-drug interactions and liver toxicity of drugs for COVID-19 treatment.
- **International Harmonization:** OCP representatives play a lead role in several ICH activities, including: ICH M10 - Bioanalytical Method Validation Expert Working Group (EWG); ICH E14/S7B IWG – Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential: The E14/S7B implementation working group; ICH M12 – Drug Interactions M12 EWG; and ICH M15 – Model-Informed Drug Development informal Working Group - General Considerations for Model-Informed Drug Development (MIDD). OCP staff also played a prominent role in the Global Bioequivalence Harmonisation Initiative,* facilitating international scientific and regulatory discussions on bioequivalence (BE) issues including statistical considerations, fed versus fasting in BE trials, and BE studies of topical and narrow therapeutic index drugs.
- **Memoranda of Understanding (MOUs):** OCP cooperated with multiple institutions to create opportunities for collaborative research and education under FDA MOUs—formal agreements between the FDA and federal, state, or local government agencies; academic institutions; and other entities (e.g., non-profit organizations).
- **The Pediatric Cluster:** OCP actively participates in The Pediatric Cluster, monthly teleconferences with international regulators to identify gaps and harmonize approaches in pediatric drug development. These exchanges enhance the science of pediatric trials to avoid exposing children to unnecessary trials, provide a robust ethical and scientific framework for pediatric studies, and benefit from the clinical pharmacology perspectives shared by our staff.

*Not an ICH-sponsored initiative

Spotlight On Innovation: Patient-Centric Communication Strategies

OCP continues to develop innovative health communication and outreach strategies to engage, educate, learn from, and collaborate with patients, caregivers, and healthcare providers.

- **Engaging Pharmacy Education Institutions:** OCP identified opportunities to dialog with U.S. pharmacy schools about emerging trends in drug development and technical skills needed for future pharmacists. The goal is for OCP to better understand current clinical pharmacy practice and explore joint educational opportunities. In 2022, OCP's Labeling and Health Communication (LHC) staff engaged with the University of Georgia and Virginia Commonwealth University Schools of Pharmacy, with plans to expand collaboration to other institutions, including internationally with European regulators and universities. This academic forum was used to obtain user feedback on a novel educational media-based tool on cytochrome P450 (CYP) and transporter-based interactions for students pursuing degrees in health professions. Feedback from these interactions was used to optimize this tool for students and other healthcare providers.
- **Public-Directed Outreach and Education:** OCP has identified areas where public outreach may provide a positive impact on public health through enhanced understanding of clinical pharmacology topics, such as the relevance of drug-drug and food-drug interactions or organ impairment in patient response to treatment. Development of materials optimized for the general public is essential to this enhanced understanding. In 2022, OCP LHC led an interdisciplinary working group to optimize the highly utilized public facing FDA web resources for drug interaction information. This group continues to update web resources with current drug interaction information and is implementing design enhancements to make them more engaging and useful to the public, including use of innovative graphics and media tools. Given the frequency of CYP-based interactions and warnings provided in direct-to-consumer advertising, a better understanding of these drug interactions will have a direct impact on public safety. OCP also plans to utilize its academic forums to identify and provide feedback on these materials given their robust outreach programs to underserved communities.

> **"We strive every day to translate the great work we do in OCP into health communications that are actionable and useful to the healthcare provider and ultimately protect the public through optimal dosing, mitigation of preventable risk, and ensuring the safe and effective use of drugs in the broadest population possible."**
>
> **Joseph Grillo, PharmD**
> Associate Director for Labeling and Health Communication

2023 Outlook

Our 5-year strategic plan is the result of a rigorous grassroots effort led by our staff. Through introspection, engagement with our partners, and robust horizon scanning, we developed a strategy for how to best position OCP in service of patients, ensure scientific excellence, and support our world-class staff. In 2023, we will use our strategic plan to advance the science of clinical pharmacology to benefit patients throughout our drug evaluation, policy, research, and engagement functions. We will continue to deliver on our mission-critical functions as well as foster innovation in drug development through regulatory programs such as the MIDD Paired Meeting Program, the ARC program, our robust regulatory science program, and collaborative engagements, among other key programs and activities. We will continue to address urgent public health challenges that have a direct impact on patients.

OCP staff aspire to remain at the forefront of innovative approaches that have the potential to improve drug efficacy and safety and enhance patient lives. We are committed to working collaboratively to ensure a shared vision based on the most up-to-date science and the voice of patients.

The authorization of novel regulatory and scientific programs under PDUFA VII and the finalization of our strategic plan at the end of 2022 position OCP to be ready on all fronts to champion innovation across our organization in 2023. We look forward to the successful development of novel tools, programs, approaches, and engagements that will help streamline drug development and bring safe and effective drugs to the public.

Examples presented in this Annual Report are illustrative and are not a comprehensive representation of our 2022 activities and accomplishments. For comments or questions, please contact ocp@fda.hhs.gov.

Appendix

OCP Publications for 2022

Publication Title	Citation
2021 white paper on recent issues in bioanalysis: ISR for biomarkers, liquid biopsies, spectral cytometry, inhalation/oral & multispecific biotherapeutics, accuracy/LLOQ for flow cytometry (Part 2 --recommendations on biomarkers/CDx assays development & validation, cytometry validation & innovation, biotherapeutics PK LBA regulated bioanalysis, critical reagents & positive controls generation)	Bioanalysis 2022 May;14(10):627-92.
2021 white paper on recent issues in bioanalysis: TAb/NAb, viral vector CDx, shedding assays; CRISPR/Cas9 & CAR-T immunogenicity; PCR & vaccine assay performance; ADA assay comparability & cut point appropriateness (Part 3--recommendations on gene therapy, cell therapy, vaccine assays; immunogenicity of biotherapeutics and novel modalities; integrated summary of immunogenicity harmonization)	Bioanalysis 2022 Jun;14(11):737-93.
2021 white paper on recent issues in bioanalysis: mass spec of proteins, extracellular vesicles, CRISPR, chiral assays, oligos; nanomedicines bioanalysis; ICH M10 section 7.1; non-liquid & rare matrices; regulatory inputs (Part 1A--recommendations on endogenous compounds, small molecules, complex methods, regulated mass spec of large molecules, small molecule, PoC & Part 1B--regulatory agencies' inputs on bioanalysis, biomarkers, immunogenicity, gene & cell therapy and vaccine)	Bioanalysis 2022 May;14(9):505-80.
A network paradigm predicts drug synergistic effects using downstream protein-protein interactions	CPT Pharmacometrics Syst Pharmacol 2022 Nov;11(11):1527-38.
A randomized, cross-over trial of metoprolol succinate formulations to evaluate PK and PD endpoints for therapeutic equivalence	Clin Transl Sci 2022 Jul;15(7):1764-75.
A tribute to the pioneers of fetal pharmacology	J Clin Pharmacol 2022 Sep;62 Suppl 1:S12-7.
Acute hyperkinetic movement disorders as a multifactorial pharmacodynamic drug interaction between methylphenidate and risperidone in children and adolescents	J Clin Psychopharmacol 2022 May-Jun;42(3):238-46.
Acute pain pathways: protocol for a prospective cohort study	BMJ Open 2022 Jul 5;12(7):e058782.
Analysis of secondary pharmacology assays received by the US Food and Drug Administration	J Pharmacol Toxicol Methods 2022 Sep-Oct;117:107205.
Anti-drug antibody validation testing and reporting harmonization	AAPS J 2022 Feb;24(1):4.
Application of machine learning based methods in exposure-response analysis	J Pharmacokinet Pharmacodyn 2022 Aug;49(4):401-10.
Application of modeling and simulation to identify a shortened study duration and novel bioequivalence metric for a long-acting intrauterine system	AAPS J 2022 May 2;24(3):63.
Application of population pharmacokinetic modeling, exposure-response analysis, and classification and regression tree analysis to support dosage regimen and therapeutic drug monitoring of plazomicin in complicated urinary tract infection patients with renal impairment	Antimicrob Agents Chemother 2022 Apr 19;66(4):e0207421.

Publication Title	Citation
Application of solubility and dissolution profile comparison for prediction of gastric pH-mediated drug-drug interactions	AAPS J 2022 Feb 14;24(1):35.
Applications, challenges, and outlook for PBPK modeling and simulation: a regulatory, industrial and academic perspective	Pharm Res 2022 Aug;39(8):1701-31.
Assessing abuse liability using read-across and structural alerts	Int J Toxicol 2022 Jan-Feb;41(1):76.
Assessing the use of noninvasive biomarkers in drug development for noncirrhotic nonalcoholic steatohepatitis (NASH)	Clin Pharmacol Ther 2022 Mar;111(S1):S30.
Assessment of the immunogenicity potential for oligonucleotide-based drugs	Nucleic Acid Ther 2022 Oct;32(5):369-77.
Biowaiver monograph for immediate-release solid oral dosage forms: sitagliptin phosphate monohydrate	J Pharm Sci 2022 Jan;111(1):2-13.
Biowaiver monograph for immediate-release dosage forms: levamisole hydrochloride	J Pharm Sci 2022 Dec 21 [Epub ahead of print].
Biowaiver monograph for immediate-release solid oral dosage forms: levocetirizine dihydrochloride	J Pharm Sci 2022 Dec 26 [Epub ahead of print].
Calibration and validation of a mechanistic COVID-19 model for translational quantitative systems pharmacology--a proof-of-concept model development for remdesivir	Clin Pharmacol Ther 2022 Oct;112(4):882-91.
Call to action for improving oral anticancer agent adherence	J Clin Oncol 2022 Apr 1;40(10):1036-40.
Canine intestinal organoids in a dual-chamber permeable support system	J Vis Exp 2022 Mar 2;181:e63612.
Cannabis for medical use: clinical pharmacology perspectives on scientific and regulatory challenges	Clin Pharmacol Ther 2022 Apr;111(4):732-5.
Cefiderocol dosing for patients receiving continuous renal replacement therapy	Clin Pharmacol Ther 2022 Nov;112(5):1004-7.
Changing the drug development and therapeutic paradigm with biologic drug combinations and bispecifics: how to choose between these two approaches?	Clin Transl Sci 2022 Sep;15(9):2096-104.
Characterization of dissolution-permeation system using hollow fiber membrane module and utility to predict in vivo drug permeation across BCS classes	J Pharm Sci 2022 Nov;111(11):3075-87.
Chronic cardiotoxicity assays using human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs)	Int J Mol Sci 2022 Mar 16;23(6):3199.
Cinical implications of altered drug transporter abundance/function and PBPK modeling in specific populations: an ITC perspective	Clin Pharmacol Ther 2022 Sep;112(3):501-26.
Clinical pharmacology considerations for the approval of belimumab for the treatment of adult patients with active lupus nephritis: a regulatory perspective	Lupus 2022 Apr;31(4):424-32.
Clinical pharmacology in drug development for rare diseases in neurology: contributions and opportunities	Clin Pharmacol Ther 2022 Apr;111(4):786-98.
Clinical pharmacology information in regulatory submissions and labeling: a comparative analysis of orphan and non-orphan drugs approved by the FDA	Clin Transl Sci 2022 Nov;15(11):2583-96.
Clinical pharmacology of entacapone (Comtan) from the FDA reviewer	Int J Neuropsychopharmacol 2022 Jul;25(7):567-75.

Publication Title	Citation
Clinical pharmacology of RNAi-based therapeutics: a summary based on FDA-approved small-interfering RNAs	Drug Metab Dispos 2022 Nov 4 [Epub ahead of print].
Clinical pharmacology postmarketing studies: a US FDA evaluation of knowledge gaps and translation into labeling	Clin Pharmacol Ther 2022 Mar;111(S1):S66-7.
Clinical relevance of hepatic and renal P-gp/BCRP inhibition of drugs: an International Transporter Consortium perspective	Clin Pharmacol Ther 2022 Sep;112(3):573-92.
Concentration-response model of immediate release oxycodone drug liking by different routes of abuse	Pain Med 2022 Jul;23(7):1311-22.
Considerations and challenges in the remdesivir COVID-19 pediatric development program	J Clin Pharmacol 2022 Sep 23 [Epub ahead of print].
Considerations for the forced expiratory volume in 1 second (FEV1)-based comparative clinical endpoint bioequivalence studies for orally inhaled drug products	Clin Pharmacol Ther 2022 Nov;112(5):982-9.
Considerations for use of pharmacodynamic biomarkers to support biosimilar developmen--(I) a randomized trial with PCSK9 inhibitors	Clin Pharmacol Ther 2022 Oct 25 [Epub ahead of print].
Considerations for use of pharmacodynamic biomarkers to support biosimilar development--(II) a randomized trial with IL-5 antagonists	Clin Pharmacol Ther 2022 Oct 2 [Epub ahead of print].
Considerations for use of pharmacodynamic biomarkers to support biosimilar development--(III) a randomized trial with interferon beta-1a products	Clin Pharmacol Ther 2022 Nov 2 [Epub ahead of print].
Corrigendum to "Bringing safe and effective therapies to premenopausal women with breast cancer: efforts to broaden eligibility criteria" [Annals of Oncology 32 (2021) 950-953]	Ann Oncol 2022 Mar;33(3):356.
Cross-study safety analysis of risk factors in CAR T cell clinical trials: an FDA database pilot project	Mol Ther Oncolytics 2022 Dec 15;27:182-94.
Current approaches for dissolution similarity assessment, requirements, and global expectations	AAPS J 2022 Mar 29;24(3):50.
Current perspective on residual knowledge gaps in the assessment of transporter-mediated drug interactions	Clin Pharmacol Ther 2022 Sep;112(3):450-2.
Current state and challenges of physiologically based biopharmaceutics modeling (PBBM) in oral drug product development	Pharm Res 2022 Sep 8 [Epub ahead of print].
Current status and future directions for a neurotoxicity hazard assessment framework that integrates in silico approaches	Comput Toxicol 2022 May;22:100223.
Deep learning models for predicting gas adsorption capacity of nanomaterials	Nanomaterials 2022 Sep 27;12(19):3376.
DeepCausality: a general AI-powered causal inference framework for free text: a case study of LiverTox	Front Artif Intell 2022 Dec 6;5:999289.
Determination of five positive control drugs in hERG external solution (buffer) by LC-MS/MS to support in vitro hERG assay as recommended by ICH S7B	J Pharmacol Toxicol Methods 2022 Nov-Dec;118:107229.
Developing an in vitro to in vivo extrapolation (IVIVE) model to predict human milk-to-plasma drug concentration ratios	Mol Pharm 2022 Jul 4;19(7):2506-17.
Development of a translational model to assess the impact of opioid overdose and naloxone dosing on respiratory depression and cardiac arrest	Clin Pharmacol Ther 2022 Nov;112(5):1020-32.

Publication Title	Citation
Development of QSAR models to predict blood-brain barrier permeability	Front Pharmacol 2022 Oct 20;13:1040838.
Dissolution-hollow fiber membrane (D-HFM) system to anticipate bio-pharmaceutics risk of tablets and capsules	J Pharm Sci 2022 Oct 4 [Epub ahead of print].
Do differences in cell lines and methods used for calculation of IC(50) values influence categorization of drugs as P-glycoprotein substrates and inhibitors?	Xenobiotica 2022 Oct 11 [Epub ahead of print].
Dose-finding studies in drug development for rare genetic diseases	Orphanet J Rare Dis 2022 Apr 5;17(1):156.
Effect of oral ranitidine on urinary excretion of N-nitrosodimethylamine (NDMA)	Clin Pharmacol Ther 2022 Mar;111(S1):S76.
Effect of paroxetine or quetiapine combined with oxycodone vs oxycodone alone on ventilation during hypercapnia: a randomized clinical trial	JAMA 2022 Oct 11;328(14):1405-14.
Efficient model-based bioequivalence testing	Biostatistics 2022 Jan;23(1):314-27.
Emerging technologies and their impact on regulatory science	Adv Exp Med Biol 2022 Jan;247(1):1-75.
Evaluating the utility of proteomics for the identification of circulating pharmacodynamic biomarkers of IFNbeta-1a biologics	Clin Pharmacol Ther 2022 Oct 29 [Epub ahead of print].
Evaluation of a sequential antibiotic treatment regimen of ampicillin, ciprofloxacin and fosfomycin against Escherichia coli CFT073 in the hollow fiber infection model compared with simultaneous combination treatment	Antibiotics 2022 Nov 26;11(12):1705.
Evaluation of gastric pH-dependent drug interactions with acid-reducing agents for orally administered oncology drugs--current status and further assessments	Clin Pharmacol Ther 2022 Mar;111(S1):S33-4.
Evaluation of glucose administration recommendation in bioequivalence studies to support generic oral antidiabetic drug development	Clin Pharmacol Ther 2022 Mar;111(S1):S80.
Evidence, in context: a regulatory perspective on pharmacogenetics	Clin Pharmacol Ther 2022 Jun;111(6):1202-4.
Exogenous sex hormones and sex hormone receptor modulators in COVID-19--rationale and clinical pharmacology considerations	Clin Pharmacol Ther 2022 Mar;111(3):559-71.
Expanding approved patient populations for rare disease treatment using in vitro data	Clin Pharmacol Ther 2022 Jul;112(1):58-61.
Experimental factors that impact CaV1.2 channel pharmacology--effects of recording temperature, charge carrier, and quantification of drug effects on the step and ramp currents elicited by the "step-step-ramp" voltage protocol	PLoS One 2022 Nov 23;17(11):e0276995.
Exploring the knowledge gaps in infant drug exposure from human milk: a clinical pharmacology perspective	J Clin Pharmacol 2022 Nov 10 [Epub ahead of print].
Extrapolation of adult efficacy data to pediatric systemic lupus erythematosus	J Clin Pharmacol 2022 Aug 15 [Epub ahead of print].
Extrapolation of efficacy from adults to pediatric patients of drugs for treatment of Partial Onset Seizures (POS): a regulatory perspective	Clin Pharmacol Ther 2022 Oct;112(4):853-63.
FDA approval summary: belantamab mafodotin for patients with relapsed or refractory multiple myeloma	Clin Cancer Res 2022 Nov 1;28(21):4629-33.
FDA approval summary: belumosudil for adult and pediatric patients 12 years and older with chronic GVHD after two or more prior lines of systemic therapy	Clin Cancer Res 2022 Jun 15;28(12):2488-92.

Publication Title	Citation
FDA approval summary: belzutifan for von Hippel-Lindau disease associated tumors	Clin Cancer Res 2022 Nov 14;28(22):4843-8.
FDA approval summary: cabozantinib for differentiated thyroid cancer	Clin Cancer Res 2022 Oct 1;28(19):4173-7.
FDA approval summary: capmatinib and tepotinib for the treatment of metastatic NSCLC harboring MET exon 14 skipping mutations or alterations	Clin Cancer Res 2022 Jan;28(2):249-54.
FDA approval summary: crizotinib for pediatric and young adult patients with relapsed or refractory systemic anaplastic large cell lymphoma	Pediatr Blood Cancer 2022 Aug;69(8):e29602.
FDA approval summary: decitabine and cedazuridine tablets for myelodysplastic syndromes	Clin Cancer Res 2022 Aug 15;28(16):3411-6.
FDA approval summary for lonafarnib (Zokinvy) for the treatment of Hutchinson-Gilford progeria syndrome and processing-deficient progeroid laminopathies	Genet Med 2022 Dec 12 [Epub ahead of print].
FDA approval summary: ivosidenib for the treatment of patients with advanced unresectable or metastatic, chemotherapy refractory cholangiocarcinoma with an IDH1 mutation	Clin Cancer Res 2022 Jul 1;28(13):2733-7.
FDA approval summary: lutetium Lu 177 vipivotide tetraxetan for patients with metastatic castration-resistant prostate cancer	Clin Cancer Res 2022 Dec 5 [Epub ahead of print].
FDA approval summary: margetuximab plus chemotherapy for advanced or metastatic HER2-positive breast cancer	Clin Cancer Res 2022 Apr 15;28(8):1487-92.
FDA approval summary: mobocertinib for metastatic non-small cell lung cancer with EGFR exon 20 insertion mutations	Clin Cancer Res 2022 Sep 16 [Epub ahead of print].
FDA approval summary: nivolumab in combination with ipilimumab for the treatment of unresectable malignant pleural mesothelioma	Clin Cancer Res 2022 Feb;28(3):446-51.
FDA approval summary: oral azacitidine for continued treatment of adults with acute myeloid leukemia unable to complete intensive curative therapy	Clin Cancer Res 2022 Jul 15;28(14):2989-993.
FDA approval summary: pembrolizumab, atezolizumab, and cemiplimab-rwlc as single agents for first-line treatment of advanced/metastatic PD-L1 high NSCLC	Clin Cancer Res 2022 Jun 1;28(11):2221-8.
FDA approval summary: pemigatinib for previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or other rearrangement	Clin Cancer Res 2022 Oct 7 [Epub ahead of print].
FDA approval summary: ripretinib for advanced gastrointestinal stromal tumor	Clin Cancer Res 2022 Dec 9 [Epub ahead of print].
FDA approval summary: ruxolitinib for treatment of chronic graft-versus-host disease after failure of one or two lines of systemic therapy	Oncologist 2022 Jun;27(6):493-500.
FDA approval summary: sotorasib for KRAS G12C-mutated metastatic NSCLC	Clin Cancer Res 2022 Apr 15;28(8):1482-6.
FDA approval summary: tivozanib for relapsed or refractory renal cell carcinoma	Clin Cancer Res 2022 Feb;28(3):441-5.
FDA public workshop summary--Coccidioidomycosis (Valley Fever): considerations for development of antifungal drugs	Clin Infect Dis 2022 Jun 1;74(11):2061-6.
Fetal clinical pharmacology: a new frontier of drug safety and therapeutics	J Clin Pharmacol 2022 Sep;62 Suppl 1:S6-8.

Publication Title	Citation
Fine-tuning the relevance of molecular targets to pediatric cancer: addressing additional layers of complexity.	Clin Pharmacol Ther 2022 Oct 11 [Epub ahead of print]
Follow-up blood culture practices for gram-negative bloodstream infections in immunocompromised hosts at a large academic medical center.	Open Forum Infect Dis 2022 May;9(5):ofac173
Generic lamotrigine extended-release tablets are bioequivalent to innovator drug in fully replicated crossover bioequivalence study.	Epilepsia 2022 Oct 18 [Epub ahead of print]
Genome mining and metabolomics unveil pseudonochelin: a siderophore containing 5-aminosalicylate from a marine-derived Pseudonocardia sp. bacterium.	Org Lett 2022 Jun 10;24(22):3998-4002
hERG block potencies for 5 positive control drugs obtained per ICH E14/S7B Q&As best practices: impact of recording temperature and drug loss	J Pharmacol Toxicol Methods 2022 Sep-Oct;117:107193.
How to select the initial dose for a pediatric study?	J Biopharm Stat 2022 Dec 8 [Epub ahead of print].
How a pandemic simultaneously strengthened existing fundamentals and drove new innovations in clinical pharmacology	Clin Pharmacol Ther 2022 Dec;112(6):1141-4.
Human radiolabeled mass balance studies supporting the FDA approval of new drugs	Clin Transl Sci 2022 Nov;15(11):2567-75.
Impact of model misspecification on model-based tests in PK studies with parallel design: real case and simulation studies	J Pharmacokinet Pharmacodyn 2022 Oct;49(5):557-77.
Impact of switching on pharmacokinetics of therapeutic biologics and interchangeability assessment--a simulation study	J Clin Pharmacol 2022 Jan;62(1):36-45.
Improved GSimp: a flexible missing value imputation method to support regulatory bioequivalence assessment	Ann Biomed Eng 2022 Sep 15 [Epub ahead of print].
Improving dose-optimization processes used in oncology drug development to minimize toxicity and maximize benefit to patients	J Clin Oncol 2022 Oct 20;40(30):3489-500.
In vitro testing of sunscreens for dermal absorption: method comparison and rank order correlation with in vivo absorption	AAPS PharmSciTech 2022 Apr 22;23(5):121.
Individualized patient care through model-informed precision dosing: reflections on training future practitioners	AAPS J 2022 Nov 15;24(6):117.
Innovations in pediatric therapeutics development: principles for the use of bridging biomarkers in pediatric extrapolation	Ther Innov Regul Sci 2022 Sep 3 [Epub ahead of print].
Integration of engineered delivery with the pharmacokinetics of medical candidates via physiology-based pharmacokinetics	Methods Mol Biol 2022;2486:57-69.
IVIVE: facilitating the use of in vitro toxicity data in risk assessment and decision making	Toxics 2022 May 1;10(5):232.
Landscape analysis of the application of artificial intelligence and machine learning in regulatory submissions for drug development from 2016 to 2021	Clin Pharmacol Ther 2022 Jun 16 [Epub ahead of print].
Leveraging clinical pharmacology data to assess biosimilarity and interchangeability of insulin products	Clin Pharmacol Ther 2022 Sep 2 [Epub ahead of print].
Long-acting formulations for the prevention and treatment of human immunodeficiency virus (HIV)-1 infection: strategic leveraging and integration of multidisciplinary knowledge to advance public health	Clin Infect Dis 2022 Dec 1;75(Supplement_4):S498-501.

Publication Title	Citation
Machine learning models for predicting cytotoxicity of nanomaterials	Chem Res Toxicol 2022 Feb 21;35(2):125-39.
Medication cost-savings and utilization of generic inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA) drug products in the USA	Ther Innov Regul Sci 2022 Mar;56(2):346-57.
Model informed drug development approaches to assist new drug development in the COVID-19 pandemic	Clin Pharmacol Ther 2022 Mar;111(3):572-8
Model-based approach to selecting pegfilgrastim dose for pharmacokinetic and pharmacodynamic similarity studies in biosimilar development	Clin Pharmacol Ther 2022 Jul 29 [Epub ahead of print].
Model-informed approach supporting approval of adalimumab (HUMIRA) in pediatric patients with ulcerative colitis from a regulatory perspective	AAPS J 2022 Jul 6;24(4):79.
Model-informed approach supporting drug development and regulatory evaluation for rare diseases	J Clin Pharmacol 2022 Dec;62 Suppl 2:S27-37.
Modeling clinical phenotype variability: consideration of genomic variations, computational methods, and quantitative proteomics	J Pharm Sci 2022 Oct 21 [Epub ahead of print]
More than pharmacokinetics: transporters in clinical pharmacology	Clin Pharmacol Ther 2022 Sep;112(3):423-6.
Ontology-based classification and analysis of adverse events associated with the usage of chloroquine and hydroxychloroquine	Front Pharmacol 2022 Mar 23;13:812338.
Orthopedic Coordinated Registry Network (Ortho-CRN): advanced infrastructure for real-world evidence generation	BMJ Surg Interv Health Technol 2022 Nov 11;4(Suppl 1):e000073.
Pairwise comparison of hydrochlorothiazide and chlorthalidone responses among hypertensive patients	Clin Transl Sci 2022 Oct 21 [Epub ahead of print].
Participation of older adults in clinical trials for new drug applications and biologics license applications from 2010 through 2019	JAMA Netw Open 2022 Oct;5(10):e2236149.
Pediatric and adult placebo response rates in placebo-controlled clinical trials submitted to the US FDA 2012-2020	J Clin Pharmacol 2022 Aug;62(8):970-82.
Pediatric drug development studies for familial hypercholesterolemia submitted to the US Food and Drug Administration between 2007-2020	J Clin Pharmacol 2022 Mar;62(3):397-408.
Pediatric efficacy extrapolation in drug development submitted to the US Food and Drug Administration 2015-2020	J Clin Pharmacol 2022 Sep 23 [Epub ahead of print].
Perspectives on the evaluation and adoption of complex in vitro models in drug development: workshop with the FDA and the pharmaceutical industry (IQ MPS Affiliate)	ALTEX 2022;39(2):297-314
Pharmacodynamic biomarkers evidentiary considerations for biosimilar development and approval	Clin Pharmacol Ther 2022 Sep 30 [Epub ahead of print].
Pharmacodynamic biomarkers for biosimilar development and approval: a workshop summary	Clin Pharmacol Ther 2022 Nov 15 [Epub ahead of print].
Pharmacokinetics of cefazolin in patients with obesity undergoing surgery requiring cardiopulmonary bypass	J Cardiothorac Vasc Anesth 2022 Aug;36(8 Pt B):2942-7.
Population pharmacokinetics of moxifloxacin in children	Paediatr Drugs 2022 Mar;24(2):163-73.
Pregnancy associated adverse events in patients treated with therapies for COVID-19 reported to the FDA ACMT COVID-19 ToxIC (FACT) pharmacovigilance project	Clin Toxicol 2022;60(Suppl. 2):18.

Publication Title	Citation
Premarket assessment of molecular alterations in drug targets: a case study of 2020 drug approvals	Pharmacogenomics 2022 May;23(7):397-404.
Prescriber perspectives on biosimilar adoption and potential role of clinical pharmacology: a workshop summary	Clin Pharmacol Ther 2022 Oct 17 [Epub ahead of print].
Promoting clinical trial diversity: a highlight of select U.S. FDA initiatives	Clin Pharmacol Ther 2022 Dec 13 [Epub ahead of print].
Quantitative methods and modeling to assess COVID-19-interrupted in vivo pharmacokinetic bioequivalence studies with two reference batches	CPT Pharmacometrics Syst Pharmacol 2022 Jul;11(7):833-42.
Racial and ethnic differences in drug disposition and response: review of new molecular entities approved between 2014 and 2019	J Clin Pharmacol 2022 Apr;62(4):486-93.
Rationale for dosage adjustment of Lefamulin in patients with hepatic impairment: increase in free drug exposure	Clin Pharmacol Ther 2022 Mar;111(S1):S9.
Recommendations for dose selection for adolescent patients in relevant adult oncology clinical trials	Clin Pharmacol Ther 2022 Apr;111(4):956-63.
Regulatory utility of physiologically based pharmacokinetic modeling to support alternative bioequivalence approaches and risk assessment: a workshop summary report.	CPT Pharmacometrics Syst Pharmacol 2022 Dec 18 [Epub ahead of print]
Reply to White et al	Clin Infect Dis 2022 Jul 15;75(2):359.
Retrospective analysis of clinical trial safety data for pembrolizumab reveals the effect of co-occurring infections on immune-related adverse events	PLoS One 2022 Feb 10;17(2):e0263402.
Review: Role of model-informed drug development approaches in the lifecycle of drug development and regulatory decision-making	Pharm Res 2022 Aug;39(8):1669-80.
Risk assessment of nanocrystal formulated zileuton (a poorly soluble BCS-II oral drug) using in vivo model	Toxicol Lett 2022 Sep 1;368(Suppl.):S278.
Roadmap to 2030 for drug evaluation in older adults	Clin Pharmacol Ther 2022 Aug;112(2):210-23.
Scientific and regulatory activities initiated by the U.S. Food and Drug Administration to foster approvals of generic dry powder inhalers: bioequivalence perspective	Adv Drug Deliv Rev 2022 Nov;190:114526.
Scientific and regulatory activities initiated by the U.S. Food and Drug Administration to foster approvals of generic dry powder inhalers: quality perspective	Adv Drug Deliv Rev 2022 Oct;189:114519.
Significance of the vitamin D receptor on crosstalk with nuclear receptors and regulation of enzymes and transporters	AAPS J 2022 Jun 1;24(4):71.
The importance of diversity in clinical trials	Clin Pharmacol Ther 2022 Jul 22 [Epub ahead of print].
The influence of pharmaceutical care in patients with advanced non-small-cell lung cancer receiving combination cytotoxic chemotherapy and PD-1/PD-L1 inhibitors	Front Pharmacol 2022 Oct 18;13:910722.
The use of physiologically based pharmacokinetic analyses--in biopharmaceutics applications -regulatory and industry perspectives	Pharm Res 2022 Aug;39(8):1681-700.
Toward bridging unmet medical need in early Alzheimer's disease: an evaluation of beta-amyloid (Abeta) plaque burden as a potential drug development tool	Clin Pharmacol Ther 2022 Apr;111(4):728-31.

Publication Title	Citation
Transporters in regulatory science: notable contributions from Dr. Giacomini in the past two decades	Drug Metab Dispos 2022 Sep 1;50(9):1211-7.
Two-year analysis of national poison data system fatalities attributed to methamphetamine	Clin Toxicol 2022;60(Suppl. 2):140-1.
Use of human iPSC-CMs in nonclinical regulatory studies for cardiac safety assessment	Toxicol Sci 2022 Sep 13 [Epub ahead of print].
Utility of islet autoantibodies as enrichment biomarkers in type 1 diabetes clinical studies: a viewpoint from the FDA	Diabetologia 2022 Dec 21 [Epub ahead of print].
Utilization characteristics for COPD inhaled medication users in the Sentinel Distributed Database	Am J Respir Crit Care Med 2022 May 1;205(Suppl.):A2779.
Utilizing endogenous biomarkers to derisk assessment of transporter mediated drug-drug interactions: a scientific perspective	J Clin Pharmacol 2022 Dec;62(12):1501-6.
Whole body PBPK modeling of remdesivir and its metabolites to aid in estimating active metabolite exposure in the lung and liver in patients with organ dysfunction	Clin Pharmacol Ther 2022 Mar;111(3):624-34.

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10903 New Hampshire Ave.
Silver Spring, MD 20993
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