U.S. FOOD & DRUG ADMINISTRATION

OFFICE OF CLINICAL PHARMACOLOGY

Annual Report

Advancing the Science of Drug Response

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TABLE OF CONTENTS

Examples presented in this Annual Report are illustrative and are not a comprehensive representation of 2018 information. For detailed information on the content of this report or our Office's other activities, please contact *ocp@fda.hhs.gov*.

DIRECTOR'S MESSAGE

In 2018, we saw a public health landscape that necessitated complex, science-based, and often expedited regulatory decision-making for the benefit of patients. Paucity of innovative new treatments in areas of unmet medical need remained a challenge. The need for rigorous, but pragmatic drug development in rare diseases could not be more evident. The national opioid crisis precipitated important regulatory science and review activities to address a wide-ranging set of issues in pain management, management of opioid use disorder, and evaluation of putative controlled substances. The call by patient communities, drug developers, regulators, and other stakeholders to advance regulatory science and innovation in product development and evaluation reached a threshold level as we worked to implement provisions of the FDA Reauthorization Act of 2017, Prescription Drug User Fee Act VI (PDUFA VI). These are but a few of the realities we faced in 2018 as we created new regulatory frameworks for incorporating innovation into the review process, leveraged cutting-edge scientific methods to deal with emergent public health threats, developed practical guidance and policies, and continued our focus on continuous organizational quality improvement and growth.

The Office of Clinical Pharmacology's (OCP's) mission is two-fold: 1) play a pivotal role in advancing development of innovative new medicines by applying state-of-the-art scientific principles; and 2) promote therapeutic optimization and individualization through best practices in research, policy development, and drug evaluation throughout the product lifecycle. We accomplish our mission by:

- Generating, evaluating, and using knowledge of drug disposition, pharmacology, and disease biology to progressively reduce regulatory uncertainty and inform public health decision-making;
- Employing mechanistic and model-informed drug development (MIDD) strategies to maximize the value of early and late phase clinical drug development;
- Using experimental and analytical approaches to identify, account for, and ultimately predict patient variability in drug responses;
- Promoting therapeutic individualization and personalized medicine by translating knowledge of patient diversity into clinical recommendations for safe and effective drug use; and
- Conducting research to address immediate and emerging regulatory science issues that impact the development, evaluation, and utilization of new therapeutic products.

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

Our annual report highlights our staff's contributions to the Office of Translational Sciences (OTS), Center for Drug Evaluation and Research (CDER), and the Agency and their important work towards OCP's vision of improving public health by building and translating knowledge of drug-response into patient-centered regulatory decisions of the highest quality. I am honored to be a part of this dynamic, passionate group of scientists and proud of our efforts in service to public health.

Issam Zineh, PharmD, MPH, FCP, FCCP

Director - Office of Clinical Pharmacology

OUR ORGANIZATION

OCP is a dynamic, purpose-driven organization dedicated to promoting and protecting global public health through application of clinical pharmacology principles. OCP is made up of over 240 pharmacologists, pharmacists, chemists, physicians, nurses, project and program managers, and administrative professionals. Our shared vision is to improve public health by building and translating knowledge of drug-response into patient-centered regulatory decisions of the highest quality. We practice five core values that enable us to foster a culture to realize our vision: stewardship, leadership, excellence, connectedness, and diversity/respect (Figure 1). Our staff has diverse responsibilities across broad functional, therapeutic, and scientific areas (Figure 2). As our role as clinical pharmacologists in regulatory decision-making continues to evolve, we constantly assess, adapt, and advance our science and organization.

Figure 1

OCP Core Values

OCP CORE VALUES

Stewardship

We are committed to serving the public. All of our objectives and actions are aligned with public health interests.

Leadership

We use our influence to positively impact our organization, patients, and society.

Excellence

We hold ourselves to the highest ethical and scientific standards in all the work we do.

Connectedness

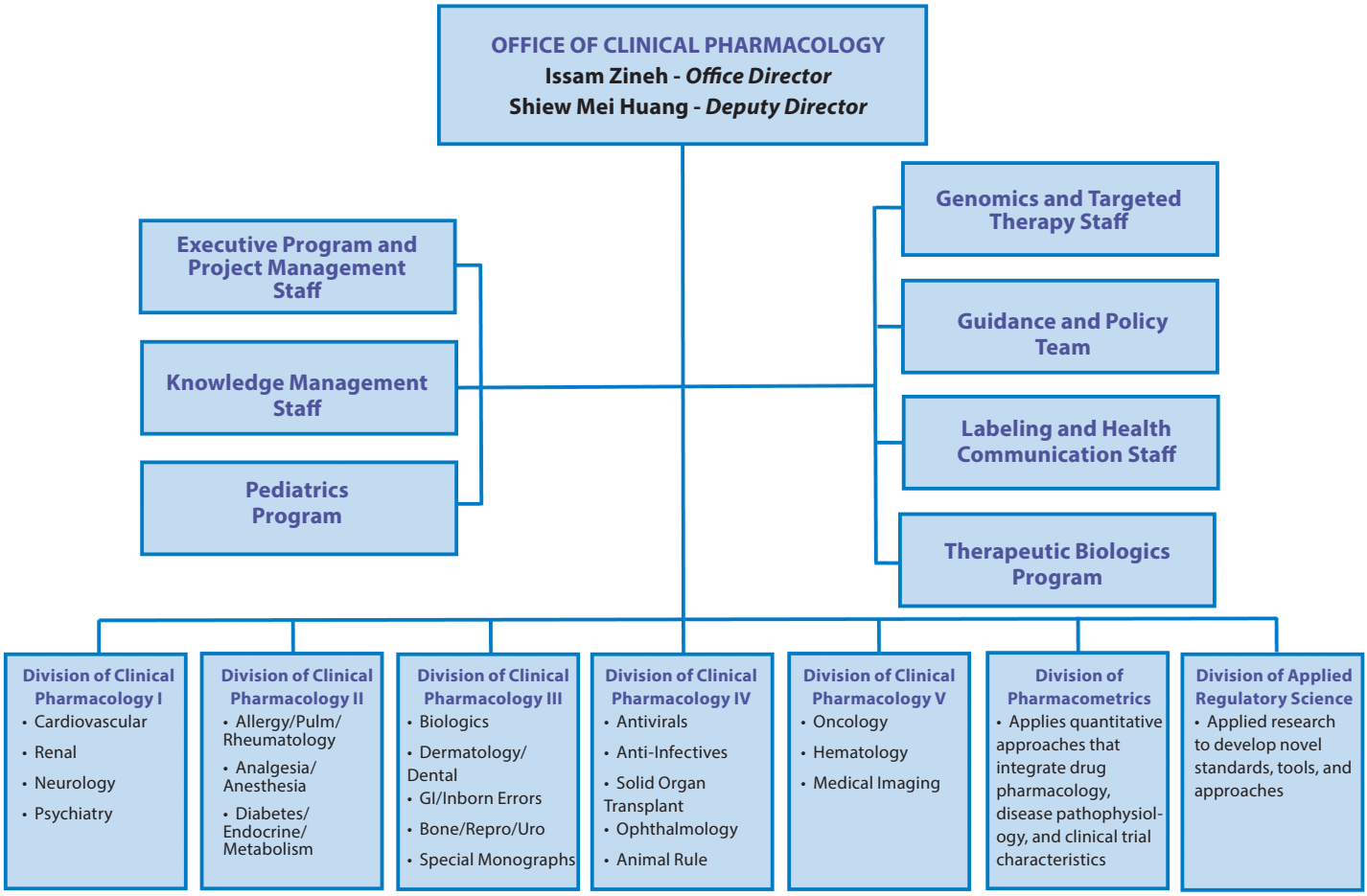
We recognize that we are members of a community. We value and foster quality interactions.

Diversity and Respect

We believe every idea is worth considering; every member of our team is important.

Figure 2

Office of Clinical Pharmacology Organizational Structure



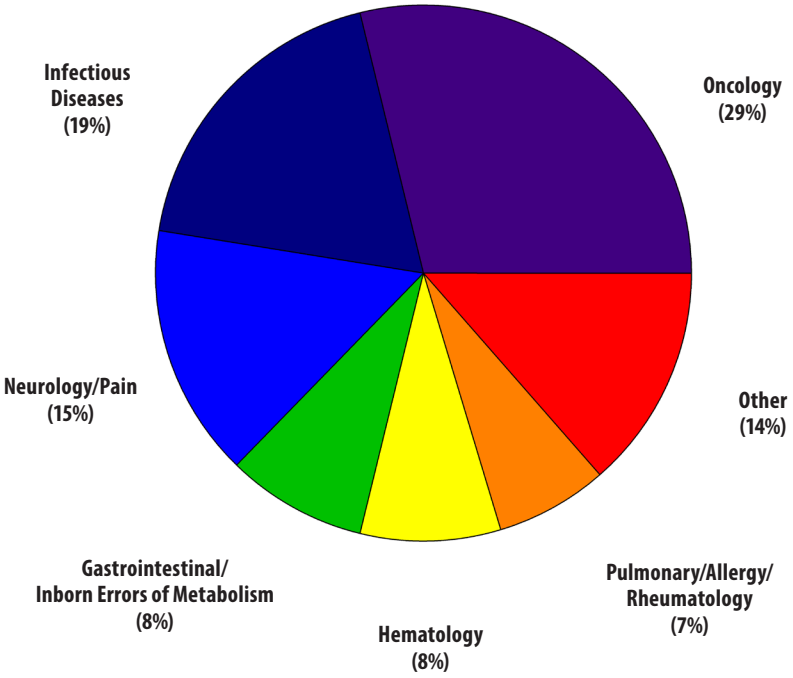
GI: Gastrointestinal
Pulm: Pulmonary
Repro: Reproduction
Uro: Urology

OCP REGULATORY REVIEW

The benefit-risk assessment of drug and biological products relies on thorough, efficient assimilation and evaluation of clinical pharmacology information. OCP supports PDUFA VI, the Biosimilar User Fee Act II (BsUFA II), and the Generic Drug User Fee Act II (GDUFA II) by conducting comprehensive assessment of clinical pharmacology information in new drug applications (NDAs), biologics license applications (BLAs), including 351(k) applications (i.e., biosimilars), and investigational new drug applications (INDs). Our interdisciplinary review process leverages our expertise to inform patient-centered regulatory decisions based on an understanding of a drug's or biologic's clinical pharmacology characteristics. In 2018, OCP contributed to the approval of 59 novel drugs and biological products across a range of indications, and many of these new products fulfilled unmet and emergent medical needs (Figure 3). In addition to novel drugs and biological products, OCP's evaluation of several non-new molecular entities, new dosage forms, and biosimilar products supported approvals to expand treatment options for patients.

Figure 3

Therapeutic Areas with Novel Product Approvals in 2018 (N=59)



NDA/BLA Review

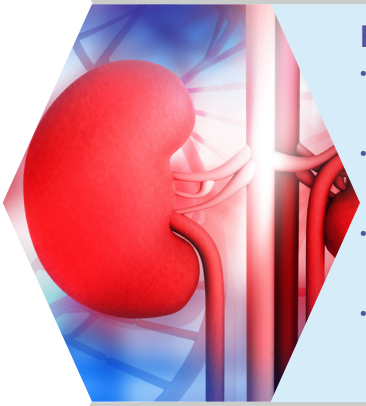
OCP provided critical reviews for NDAs and BLAs in 2018 by applying modernized regulatory review processes and innovative analytical approaches to **optimize dosing recommendations, quantify risk, develop management strategies to mitigate those risks, and guide patient selection for treatment** (Figure 4). OCP values the scientific exchange of ideas not only within CDER's multi-disciplinary review environment, but also externally in FDA advisory committee forums. Our staff participated in 14 advisory committee meetings for NDA and BLA products in 2018, presenting on dose evaluation and exposure/response (E/R)-based rationale, bioanalysis, drug interactions, titration and monitoring strategies, and benefit-risk assessment.

Figure 4

OCP Reviews of Select NDA, BLA, and Biosimilar Product Approvals in 2018

HOW WE OPTIMIZE DOSING

- **AJOVY (fremanezumab):** Recommended dosing regimens for preventive treatment of migraine in adults based on dose-efficacy/safety relationships in migraine patients.
- **LIBTAYO (cemiplimab-rwlc):** Utilized pharmacokinetic/pharmacodynamic (PK/PD) relationships to support a flat dosing regimen versus the weight-based regimen studied in clinical trials in patients with squamous cell carcinoma.
- **SEYSARA (sarecycline):** Leveraged E/R information to support weight-banded dosing regimens for treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris.
- **TAKHZYRO (lanadelumab):** Leveraged E/R information to support approval of new dosing regimen to treat patients with types I and II hereditary angioedema.
- **TPOXX (tecovirimat):** Established pediatric dosing recommendations based on PK modeling and simulation for treatment of smallpox infection under FDA's Animal Rule regulatory pathway.



HOW WE MITIGATE RISK

- **ARAKODA and KRINTAFEL (tafenoquine):** Utilized knowledge of exposure-safety relationships to harmonize labeling recommendations for two tafenoquine products with differing indications and dosing regimens.
- **TIBSOVO (ivosidenib):** Used physiologically based PK (PBPK) modeling to support dosage reductions for TIBSOVO when administered with strong cytochrome (CYP) 3A4 inhibitors in treating patients for relapsed or refractory acute myeloid leukemia.
- **YUPELRI (revefenacin):** Evaluated metabolite exposures in moderate hepatic impairment patients to support a recommendation not to use YUPELRI to treat chronic obstructive pulmonary disease patients with any degree of hepatic impairment.
- **ZEMDRI (plazomicin):** Integrated pharmacologic and E/R information from limited clinical data to inform therapeutic drug monitoring recommendations to mitigate acute kidney injury risk in patients with complicated urinary tract infections including pyelonephritis.

HOW WE GUIDE PATIENT SELECTION

- **GALAFOLD (migalastat):** Designed a labeling strategy that incorporates in vitro assay data to expand the treatment indication in adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene variant.
- **SYMDEKO (tezacaftor/ivacaftor):** Expanded cystic fibrosis (CF) indication based on in vitro data for patients 12 years or older who have two copies of the *F508del* mutation of the CF transmembrane conductance regulator gene or have at least one mutations that is responsive to the drug.
- **TIBSOVO (ivosidenib):** Informed labeling for selecting adult patients for treatment with TIBSOVO for relapsed or refractory acute myeloid leukemia based on the presence of isocitrate dehydrogenase 1 mutations in the blood or bone marrow.

IND Review and Consults

The IND review space provides OCP the opportunity to engage with drug developers and inform drug development plans. OCP reviews available clinical pharmacology data and provides recommendations on development strategies from the pre-IND stage and as development plans progress. In addition to lending clinical pharmacology expertise to drugs and biological products in development, OCP responded to consults outside the scope of normal IND review from other offices and centers throughout FDA. During 2018, consult requestors sought OCP input on general clinical pharmacology, study designs, prescription drug labeling, pharmacogenomics, safety/toxicity assessment, assay development, biomarkers, and drug-containing medical devices. Our Chemical Informatics Program provided structure-based safety assessments of non-clinical and clinical endpoints of regulatory significance, including genetic toxicity, carcinogenicity, hepatotoxicity, and cardiotoxicity, in response to 297 consults for 880 chemicals analyzed in 2018.

Model-Informed Drug Development

MIDD is defined as the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources to inform drug development and regulatory decision-making. OCP leads CDER's multidisciplinary MIDD Initiative. This initiative, established under PDUFA VI, has multiple components, and 2018 marked several accomplishments under these domains (Table 1).

Table 1

MIDD Milestones in 2018

Domain	Milestones
Regulatory Science and Review Expertise	• Strategically assessed human capital needs for MIDD program staffing • Conducted a preliminary needs assessment for internal training and implemented a structured communication plan and training program for staff
Workshops/Stakeholder Engagement	• Co-sponsored a workshop with the International Society of Pharmacometrics on MIDD for oncology products • Initiated planning for a future workshop to discuss best practices, evidentiary criteria, knowledge gaps, and research needs in the use of PBPK modeling approaches to support clinical pharmacology regulatory decision making
MIDD Pilot Program	• Launched the MIDD Pilot Program to provide an opportunity for drug developers and FDA to discuss the application of MIDD approaches to the development and regulatory evaluation of medical products in development • Led multiple interdisciplinary meetings under this program in 2018 that served as interaction points for drug developers to discuss MIDD strategies throughout all stages of drug development

Review Modernization

In 2018, CDER implemented new steps to modernize review functions by cross-disciplinary review teams to advance its public health goals. OCP supported Center-level efforts in modernization of the review process by identifying ways to streamline review, reduce redundancy, and enable timely decision-making.

1 Integration of OCP Review into CDER Review Modernization

The CDER "Unireview" is a new, multi-disciplinary approach to documenting reviewer assessments intended to reduce redundancy, increase collaboration, and promote transparency. OCP's Good Review Practices Manual of Policies and Procedures provided the principled framework of the Unireview and served as a template for incorporation of OCP's issue-based format into the Unireview for many NME approvals in 2018.

2 Modernization of OCP Labeling Review

Prescription drug labeling (PDL) is an important vehicle for communicating information to health care providers to enable safe and effective prescribing of drugs. To create consistency in describing clinical pharmacology information in PDL, and thereby enhance readability and comprehension, OCP implemented the OCP Integrated Labeling Review Process for NME NDAs and Original BLAs in 2018.

3 Cardiac QT Prolongation Risk Evaluation Paradigm Alignment

Proarrhythmic risk potential is a primary review focus of OCP. OCP continued to lead in science-based policy development for proarrhythmia risk evaluation. We additionally advanced our review approach as the QT risk evaluation paradigm evolved from primary evaluation of thorough QT studies to integrated concentration-QT-based assessments in dose-ranging studies. In 2018, OCP transitioned to a decentralized QT review work model to increase review efficiency in this evolving field.

OCP POLICY INITIATIVES

OCP's policy initiatives in 2018 underscore our commitment to our mission by 1) providing a framework for advancing innovation in drug development based on the scientific principles of clinical pharmacology, and 2) promoting therapeutic optimization and individualization. OCP issued four guidance documents in 2018 reflecting our current thinking on complex drug development issues (Table 2). We have also responded to emerging policy needs through timely initiation with the development of nine additional OCP-led guidances and continuing engagement with internal and external stakeholders to gain input on contemporary guidance topics through the Federal Register (FR) notice process.

OCP values collaborative opportunities and scientific exchange with academic, industry, and fellow regulatory scientists to inform policy and scientific initiatives, and our staff involvement on 70 internal and external committees, task forces, and working groups in 2018. Priority focus areas of working groups and committees included technology/tools/standards (22%), general drug development topics (16%), regulatory policy (15%), product/class/therapeutic-specific domains (15%), research-related (12%), general clinical pharmacology (9%), MIDD (7%), and professional development and work culture (4%).

Table 2

OCP-Led Guidances Published in 2018

Guidance	Focus
Bioanalytical Method Validation (Final)	Development, validation, and in-study use of bioanalytical methods that quantitatively determine the levels of drugs, their metabolites, therapeutic proteins, and biomarkers in biological matrices
Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease (Final)	General approaches to evaluate the benefits and risks of targeted therapies within a clinically-defined disease where some molecular alterations may occur at low frequencies
Maximal Usage Trials for Topical Active Ingredients Being Considered for Inclusion in an Over-the-Counter Monograph: Study Elements and Considerations (Draft)	Design and conduct of the Maximal Usage Trial, a standardized approach to assessing the in vivo bioavailability of topical drug products
Physiologically Based Pharmacokinetic Analyses — Format and Content (Final)	Format and content of PBPK data and analyses submitted in IND, NDA, BLA, and Abbreviated New Drug Applications (ANDA) to enable efficient and consistent FDA review

In 2018, FDA policy efforts on broader topics included substantial contribution from OCP in the areas of biopharmaceutics, biological product development, infectious diseases, oncology, rare diseases, antiseptics, and generics. OCP staff served in leadership capacities on several global policy efforts as part of the International Conference on Harmonization (ICH) (Figure 5).

BCS-Based Biowaivers (ICH M9)

Concensus guideline issued as draft in 2018, which provides recommendations to support the biopharmaceutics classification of 22 drug substances and the Biopharmaceutics Classification System (BCS)-based biowaiver of bioequivalence (BE) studies for drug products.

Bioanalytical Method Validation (ICH M10)

New multidisciplinary guideline addressing issues and criteria for the validation of bioanalytical methods and study sample analyses that support PK data obtained in non-clinical and clinical studies.

Clinical and Non-Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential (ICH E14/S7B)

Implementation working group established for the development of Q&As for ICH E14/S7B Guidelines, which describe non-clinical and clinical risk assessment strategies to inform the potential risk for proarrhythmia of a test substance and contribute to the design of clinical investigations.

Figure 5

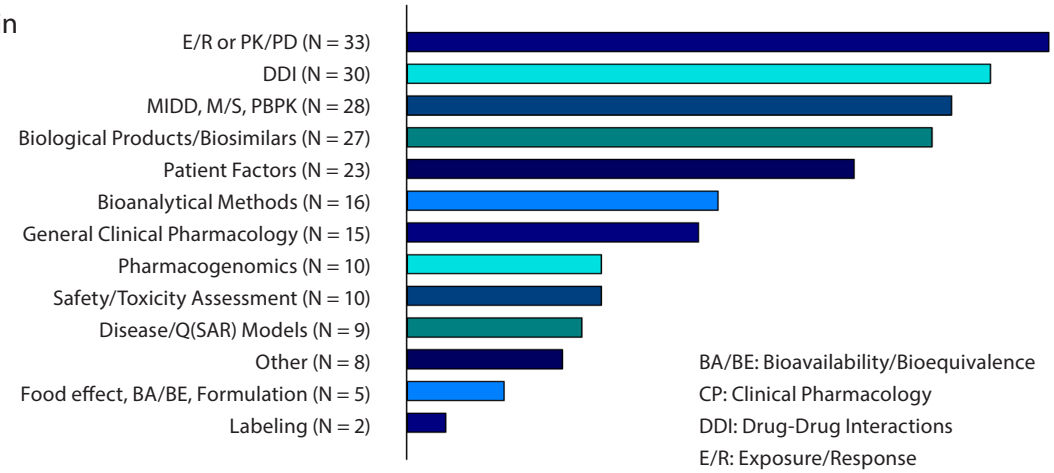
Leading International Policy Development in 2018

OCP RESEARCH

Innovative and rigorous regulatory science research provides a solid foundation for clinical pharmacology policy and review, and ultimately increases the probability of successful development of new products for medical needs. In 2018, OCP engaged in 216 research projects that focused on a wide range of research topics (Figure 6). OCP review divisions leverage their clinical pharmacology expertise to design focused and collaborative projects to inform regulatory decision-making, and OCP's dedicated research group, the Division of Applied Regulatory Science (DARS), provides resources and expertise to answer complex regulatory review questions and address urgent public health problems (Figure 7 and Table 3). DARS utilizes translational approaches, such as in vitro and in vivo laboratory methods, in silico computational modeling and informatics, and experimental medicine to advance review and basic research activities.

Figure 6

OCP Research Focus in 2018 (N = 216)



BA/BE: Bioavailability/Bioequivalence
CP: Clinical Pharmacology
DDI: Drug-Drug Interactions
E/R: Exposure/Response
M/S: Modeling and Simulation
PK/PD: Pharmacokinetics/Pharmacodynamics
Q(SAR): Quantitative Structure-Activity Relationship

Figure 7

Applied Regulatory Science: Responding to Urgent Public Health Needs

OPIOIDS, SEDATIVES, CANNIBINOIDS, & STIMULANTS

- Evaluation of combined effects of opioids and sedative psychotrophic products on respiratory depression to inform labeling
- Development and validation of Q(SAR) models to support emergency scheduling of synthetic opioids, cannabinoids, and stimulants
- Development and validation of blood-brain barrier Q(SAR) models to predict drug abuse potential
- Evaluation of racemic methadone on cardiac ion channels and ventricular myocytes

PREDICTIVE SAFETY & CARDIAC RISK

- Generation and validation of study protocols, ion channel pharmacology data, and biomarkers for Comprehensive In Vitro Proarrhythmia Assay (CiPA) proarrhythmia assessment
- Identifying exposure and patient characteristic data for Torsade de Pointes risk
- In silico metric development for assessing proarrhythmia risk under the CiPA initiative
- Investigating sub-populations of induced pluripotent stem cell (iPSC)-cardiomyocytes for predicting cardiotoxicity
- Predicting sex differences in drug-induced proarrhythmia risk

Table 3

How We Transform Public Health Through Research

Research Focus Area	Notable Projects
Application of E/R and PK/PD	• Optimizing approaches in determining PK/PD targets of β-lactam/ β-lactamase inhibitor anti-bacterial products to address emerging drug resistance • Analysis of correlation between PK and drug liking scores of abuse-deterrent opioid products
Drug-Drug Interactions	• Evaluation of in vitro metabolism- and transporter-based drug interactions with sunscreen active ingredients • Evaluation of impact of concurrent acid-reducing agents on PK of orally administered oncology drugs
MIDD, M/S, PBPK	• Evaluation of a PBPK modeling approach to predict drug concentrations in the liver and to support safety and efficacy of new drugs, particularly for liver diseases • Using model-based analysis of natural history data and biomarker vs. clinical endpoint relationships to advance drug research in Duchenne muscular dystrophy
Biological Products/Biosimilars	• Develop an in silico-based modeling tool to determine the maximal allowable bioanalytical variability for a bioanalytical method used in PK similarity of biosimilar products to reference products • Impact of polyethylene glycol variability on protein therapeutic product quality, PK, and biosimilarity assessment
Patient Factors	• Kidney function changes with aging in adults: comparison between cross-sectional and longitudinal data analyses in renal function assessment
Bioanalysis and Biopharmaceutics	• Microphysiological systems for use as drug development tools • Food effect assessment in drug development: learning from the past to inform the future
General Clinical Pharmacology	• Assessment of human systemic absorption of sunscreen ingredients • Impact of physicochemical, biochemical, other quality attributes on PK of antibody therapeutics
Pharmacogenomics	• Identifying opportunities for precision drug development in the pharmaceutical pipeline • Phenome mapping of drug target and pathway variations
Labeling	• Effect of alternative displays in approved drug labeling on comprehension, memory, and action

OCP staff members authored 126 journal articles published in 2018 across a variety of clinical pharmacology focus areas, including safety/toxicity (20%); patient factors (15%); bioanalysis (9%); food effect, bioavailability/bioequivalence (BA/BE), formulation (9%); DDI (8%); approval summaries (7%); MIDD, M/S, PBPK (7%); pharmacogenomics (6%); biological products/biosimilars (5%); general CP (5%); other (5%); and disease/Q(SAR) models (4%).

Figure 8

Influencing Through Publications: Examples in OCP's Top 3 Focus Areas in 2018

SAFETY/TOXICITY

Biomarkers of drug-induced acute kidney injury: a regulatory perspective *(Expert Opin Drug Metab Toxicol 2018 Sep;14(9):929-36)*

Mechanistic model-informed proarrhythmic risk assessment of drugs: review of the 'CiPA' initiative and design of a prospective clinical validation study *(Clin Pharmacol Ther 2018 Jan;103(1):54-66)*

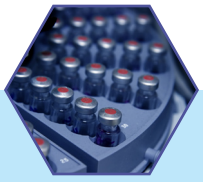
Immune response proteins as predictive biomarkers of doxorubicin-induced cardiotoxicity in breast cancer patients *(Exp Biol Med 2018 Feb;243(3):248-55)*

PATIENT FACTORS

Improving therapeutics to better care for older adults and the young: report from the American College of Clinical Pharmacology workshop *(J Clin Pharmacol 2018 Mar;58(3):277-280)*

Neonatal safety information reported to the FDA during drug development studies *(Ther Innov Regul Sci 2018 Jan;52(1):100-8)*

Pediatric drug development: outlook for science-based innovation *(Clin Pharmacol Ther 2018 Nov;104(5):785-787)*



BIOANALYSIS

Comparative evaluation of U.S. brand and generic intravenous sodium ferric gluconate complex in sucrose injection: biodistribution after intravenous dosing in rats *(Nanomaterials 2018 Jan;8(1):10)*

Hybrid assays: the next big thing? *(Bioanalysis. 2018 Jul 1;10(13):975-977)*

Novel and rapid LC-MS/MS method for quantitative analysis of methylphenidate in dried blood spots *(Bioanalysis 2018 Jun 1;10(11):839-50)*

COMMUNICATION, OUTREACH, AND ENGAGEMENT

A rapidly changing clinical pharmacology landscape necessitates efficient communication and broad outreach and engagement to keep pace with evolving science. OCP reaches a wide range of internal and external stakeholders, both domestically and internationally, through direct communication, scientific presentations, workshops, and external working group/consortia involvement.

OCP staff members gave 120 presentations at national and international meetings and conferences in 2018. Presentations focused on general clinical pharmacology (19%); safety/toxicity assessment (13%); MIDD, M/S, PBPK (10%); pharmacogenomics (10%); biological products/biosimilars (8%); patient factors (8%); bioanalysis (8%); disease/Q(SAR) models (7%); other (5%); DDI (4%); E/R or PK/PD (4%); food effect, BA/BE, formulation (2%); and labeling (2%) (Figure 9 and Figure 10).

Figure 9

OCP Presentations in 2018 (N = 120)

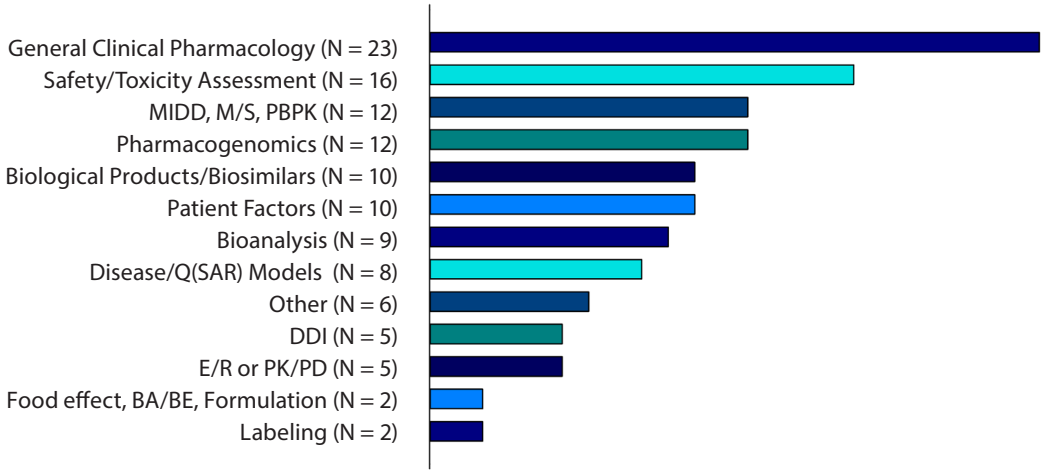
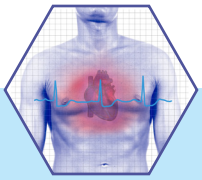


Figure 10

Influencing Through Presentations: Examples in OCP's Top 3 Focus Areas in 2018

GENERAL CLINICAL PHARMACOLOGY

- Translating New Science into Medical Product Development & Evaluation
- The Need for Collaborations and Real-World Data: Clinical Pharmacology Perspective
- Clinical Pharmacology Driving Innovation in Drug Development and Drug Approval for All Patients
- FDA's OCP: Translating Patient Diversity into Optimal Drug Therapy



SAFETY/TOXICITY

- Evaluating the Need for Developing Sex-Specific In Silico Models for Assessing Cardiac Safety of New Drugs
- National Poison Data System and Potential FDA Informatic Analyses
- Immune-Mediated Adverse Events in Humanized Mice Receiving Checkpoint Inhibitors
- ISR: Indication and Symptom Resource

MIDD, M/S, PBPK

- Model Informed Regulatory Decisions
- FDA MIDD Pilot Program
- PBPK Modeling and Simulation in Drug Product Development and Review
- Impact of Quantitative Clinical Pharmacology on Drug Approval, Dosing Recommendations, and Clinical Trial Design
- PBPK Modeling for Absorption

OCP views workshops as an essential means of engaging stakeholders, fostering collaboration and transparency, and furthering clinical pharmacology innovation and its application to public health. Workshop involvement in 2018 was multifaceted, with OCP staff spearheading, planning, and organizing as well as participating in various workshops and symposia. These included workshops and symposia on Animal Rule, bioanalytical method validation, biosimilarity, imaging and machine learning, pediatric drug development, pharmacogenomics and personalized medicine, and regulatory science topics.

Our ability to impact public health is also enhanced by academic outreach and partnerships. We leverage FDA's Memorandum of Understanding process to create ongoing collaborative scientific relationships with academic institutions (e.g., University of Georgia and Virginia Commonwealth University), and we routinely host Doctor of Pharmacy students on rotation, policy fellows, and visiting scientists from academia. In 2018, OCP fostered awareness of collaborative opportunities with FDA through participation in the American Association of Colleges of Pharmacy's (AACP's) Pharmacy Education 2018 meeting and the AACP Catalyst program for mid-career researchers. Direct involvement in national working groups and consortia (e.g., American Association of Poison Control Centers and American College of Medical Toxicology) enables us to promote safe an effective drug use with practitioners in real time.

International Engagement: a Focus on Harmonization

In 2018, OCP actively promoted the role of clinical pharmacology in the drug development process, communicated our positions on emerging technologies that impact clinical pharmacology-related drug development, leveraged available stakeholder resources, and identified opportunities for collaboration with international agencies, practitioners, and academic researchers. OCP representation in global forums on BE and BCS, biomarker-based drug development, drug interactions, labeling, emerging technologies, and MIDD was vital in providing FDA's scientific perspective and fostering exchange of ideas in reaching international harmonization and consensus (Table 4).

Table 4

How We Transform Public Health Through International Engagement

Forum	Description
European Medicines Agency	• 10-day fellowship opportunity to share experiences, harmonize regulatory assessments, and identify need for policy development in precision medicine
Global Bioequivalence Harmonization Initiative III	• Workshop to discuss complex BE issues of interest to major agencies with an eye towards harmonization
Grand Challenges 2018	• Interagency panel discussion to provide FDA perspective on an important emerging technology (i.e., PBPK) in drug development to address world health problems
International BCS Experts	• Evaluation of public domain information and publish drug specific articles that can facilitate BCS based biowaivers, particularly in the underdeveloped regions of the world for essential medicines
Marbach Castle Drug-Drug Interaction Workshop	• Interagency presentations and panel discussion to an international audience of drug interaction experts to communicate FDA perspective on DDI and foster international harmonization
Swedish Medical Products Agency	• Interagency conference to exchange information on clinical pharmacology related policy and best practice development for the review of drug applications, with attention to labeling development and MIDD
University of Manchester	• International group of pharmacy faculty and students to promote a better understanding of the US drug approval process to international practitioners

2019 OUTLOOK AND PRIORITIES

In the coming year, OCP will continue its service-based leadership to meet public health challenges. With a multidisciplinary scientific staff, wide-ranging expertise, and effective organizational management, OCP is primed to efficiently respond to emergent health issues and an evolving drug development landscape. Our review teams, research scientists, guidance and policy experts, communication specialists, and project/program management staff will continue to work synergistically to advance translational science, identify and inform policy gaps, and strengthen approaches in drug development and regulatory practice. These activities are supported by active engagement and collaboration with external stakeholders. We aim to expand our stakeholder engagement within the FDA, with professional societies, other regulatory agencies, academic institutions, and industry, and continue our outreach efforts to promote public health through effective communication.

Important areas of focus for OCP in 2019 will include current health issues related to the opioid epidemic, antimicrobial resistance, and rare diseases. The application of pharmacogenomic information will continue to play an important role in clinical trial design and therapeutic optimization. Our office will continue to facilitate and support the advancement of biosimilar development under the reauthorized user fee programs and continue to lead the advancement of MIDD approaches in drug development under PDUFA VI. We expect to review more MIDD-related drug applications and plan to host a series of MIDD workshops and educational events in the coming year, as well as dedicate the necessary resources as our MIDD work expands. OCP commits to bringing consistency and transparency to new policy areas (e.g., MIDD and lifecycle management), and additional policy efforts will be informed through proactive and expanded engagement with external stakeholders on emerging scientific and regulatory issues.

OCP looks forward to the challenges and opportunities of 2019 in partnership with our colleagues throughout the Center, the Agency, and in the scientific and patient communities.

Abbreviations

Abbreviation	Definition
AACP	American Association of Colleges of Pharmacy
ANDA	Abbreviated New Drug Application
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BLA	Biologics License Application
BsUFA II	Biosimilar User Fee Act II
CDER	Center for Drug Evaluation and Research
CF	Cystic Fibrosis
CiPA	Comprehensive In Vitro Proarrhythmia Assay
CP	Clinical Pharmacology
CYP	Cytochrome
DARS	Division of Applied Regulatory Science
DDI	Drug-Drug Interactions
E/R	Exposure/Response
FR	Federal Register
GDUFA II	Generic Drug User Fee Act II
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IND	Investigational New Drug
iPSC	Induced Pluripotent Stem Cell
ISR	Indication and Symptom Resource
M/S	Modeling and Simulation
MIDD	Model-Informed Drug Development
NDA	New Drug Application
NME	New Molecular Entity
OCP	Office of Clinical Pharmacology
OTS	Office of Translational Sciences
PBPK	Physiologically Based Pharmacokinetic
PDUFA VI	Prescription Drug User Fee Act VI
PD	Pharmacodynamic
PDL	Prescription Drug Labeling
PK	Pharmacokinetic
Q(SAR)	Quantitative Structure-Activity Relationship
QT	QT-Interval
Repro/Uro	Reproduction/Urology

U.S. Food and Drug Administration
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